BACKGROUND INFORMATION

FOR THE MEETING OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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List of Abbreviations

Abbreviation or Term	Definition/Explanation
ADT	androgen-deprivation therapy
BCE	bone collagen equivalent
BPI-SF	Brief Pain Inventory Short Form
BMD	bone mineral density
CI	confidence interval
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
denosumab (AMG 162)	monoclonal antibody to RANKL
ECOG	Eastern Cooperative Oncology Group
FACT-G	Functional Assessment of Cancer Therapy-General
FDA	Food and Drug Administration
HRQOL	health-related quality of life
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NNT	number needed to treat
ODAC	Oncologic Drugs Advisory Committee
ONJ	osteonecrosis of the jaw
PRO	patient-reported outcomes
PSA	prostate-specific antigen
Q4W	once every 4 weeks
Q6M	once every 6 months
RANKL	RANK ligand
sBLA	supplemental Biologics License Application
SC	subcutaneous(ly)
SRE	skeletal-related event
uNTX/Cr	urine N-telopeptide corrected for urine creatinine

1. Introduction

A supplemental Biologics License Application (sBLA) was submitted by Amgen, Inc. to the Food and Drug Administration (FDA) on 27 June 2011 for a new indication for XGEVA® (denosumab, a fully human monoclonal antibody that inhibits RANK ligand [RANKL]). The proposed indication is for treatment of men with castration-resistant prostate cancer (CRPC) at high risk of developing bone metastases. Study 20050147, a pivotal phase 3, placebo-controlled study in 1432 subjects with CRPC at high risk of developing bone metastases, provides the basis for this new indication. In this study, denosumab significantly prolonged median bone metastasis-free survival time (a measure of the time a patient lives without bone metastases) compared with placebo by 4.2 months with a 15% reduction in risk of developing bone metastases or death.

If approved, XGEVA® would be the first therapy licensed for men with nonmetastatic CRPC to prevent or delay bone metastases. XGEVA® was approved in November 2010 at a dose of 120 mg subcutaneously (SC) every 4 weeks (Q4W) for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors, including men with CRPC.

2. Executive Summary

Burden of Metastatic Disease

- The development of metastatic disease in men with CRPC is a life-changing event, typically dominated by bone metastases, which are irreversible and progressive, and contribute major morbidity throughout the remaining period of approximately 2 years of life.
- Bone metastases can result in incapacitating complications, which are represented by SREs including:
  - debilitating pain that can require aggressive management with radiation therapy and narcotic analgesics
  - pathologic fractures that may impair ambulation
  - surgery to prevent or treat pathologic fractures or manage pain
  - spinal cord compressions that can result in numbness or weakness, urinary or fecal incontinence, and paralysis

Denosumab in Patients With Prostate Cancer

- Denosumab is a fully human IgG2 monoclonal antibody that binds to RANKL and prevents activation of RANK, thereby inhibiting osteoclast formation, activation, and survival.
- Based on its unique mechanism of action that targets the bone microenvironment, it was hypothesized that denosumab would be of clinical benefit in multiple disease states in prostate cancer. Therefore, denosumab has been investigated in 3 large phase 3 prostate cancer clinical studies representing approximately 5000 patients:
  - **Study 20040138 in men with nonmetastatic, castration-sensitive prostate cancer to treat bone loss associated with androgen deprivation therapy (ADT).** The results of this study were the basis for the indicated use of denosumab under the proprietary name Prolia® at a dose of 60 mg SC once every 6 months (Q6M) to increase bone mass and reduce the risk of vertebral fractures.
  - **Study 20050103 in men with CRPC and established bone metastases to prevent skeletal complications (ie, SREs).** The results of this study demonstrated superiority over the previous standard of care to prevent SREs. This study, together with 2 other similar trials in breast cancer and other solid tumors, was the basis for the indicated use of denosumab under the proprietary name XGEVA® at a dose of 120 mg SC Q4W for the prevention of SREs in patients with bone metastases from solid tumors.
  - **Study 20050147 in men with nonmetastatic CRPC to prevent or delay the development of bone metastases.** This study enrolled patients at high risk of development of bone metastases based on prostate-specific antigen (PSA) criteria. The results of this pivotal study provide the evidence for the proposed new indication for XGEVA®.
  - Both Studies 20050147 and 20050103 enrolled men with CRPC; patients in Study 20050147 were selected using criteria that conferred a high risk for development of bone metastases, thus reflecting a stage of disease that immediately preceded the population studied in Study 20050103 with already established bone metastases and at risk for SREs. These studies were designed

to complement each other to provide comprehensive evidence for the activity of denosumab in preventing 1) the evolution of bone metastases from absent or undetectable micrometastases to clinically evident metastases and 2) the clinical sequelae associated with clinically evident bone metastases, including SREs. Therefore, the presence of radiologically confirmed bone metastases was the key component of the primary endpoint in Study 20050147 and was also the key study entry criterion in Study 20050103.

Men With Nonmetastatic CRPC at High Risk of Developing Bone Metastases

- Men with nonmetastatic prostate cancer undergoing ADT can be readily classified as having CRPC based on rising levels of PSA.
- Men exhibiting aggressive PSA kinetics including short PSA doubling times are at high risk for developing bone metastases within a short time period.
- Of the approximately 2.4 million men living with a history of prostate cancer in the United States, an estimated 54,000 (2%) have CRPC with a high risk of developing bone metastases.

Key Study Design Elements of Study 20050147

- Pivotal Study 20050147 was a phase 3, double-blind, international, randomized, placebo-controlled study in patients with nonmetastatic CRPC. Patients were required to be at high risk for the development of bone metastases as defined by a PSA value ≥ 8.0 ng/mL or a PSA doubling time ≤ 10.0 months at study entry.
- The intent of Study 20050147 was to confirm that denosumab could prevent bone metastases, a clinically important outcome, based on its bone-targeted mechanism of action; therefore, the focus of design and conduct of the study was on the detection of bone metastases. The primary efficacy endpoint was bone metastasis-free survival, as determined by time to first occurrence of bone metastasis (symptomatic or asymptomatic at detection) or on-study death from any cause, whichever occurred first. Death on study prior to the development of bone metastases was included in the primary endpoint in order to account for any potential imbalance in this critical outcome.
- The two secondary endpoints consisted of the time to first bone metastasis (a component of the primary endpoint) and overall survival, which included not only deaths on study (the other component of the primary endpoint) but also deaths during follow-up. Notably, as denosumab was not yet approved to treat established bone metastases during the study, subjects were required to discontinue investigational product in the presence of bone metastases to allow access to approved bone-targeting agents (ie, zoledronic acid) for the prevention of SREs. In addition, the administration of other cancer-specific therapies on study and during follow-up was permitted.

Efficacy of Denosumab in Study 20050147

Prespecified Analyses

- Denosumab significantly prolonged median bone metastasis-free survival time (primary efficacy endpoint) compared with placebo by 4.2 months with a 15% reduction in risk of developing bone metastases or death.
- Denosumab significantly prolonged median time to first bone metastasis (secondary efficacy endpoint) compared with placebo by 3.7 months with a 16% risk reduction.

- Overall survival (secondary efficacy endpoint) was similar (hazard ratio of 1.01) between the denosumab and placebo groups. Approximately 80% of deaths occurred during follow-up (off investigational product) and the median time from bone metastasis to death was approximately 19 months in both treatment arms.
- Fewer subjects in the denosumab group (9.6%) developed symptomatic bone metastases (exploratory efficacy endpoint) than in the placebo group (13.4%).
- Progression-free survival (exploratory efficacy endpoint) was directionally favorable (hazard ratio of 0.89) in the denosumab group compared with the placebo group; however, the difference between treatment groups did not reach statistical significance.

Additional Post-Hoc Analyses

- All patients enrolled in Study 20050147 were at high risk for development of bone metastases based on published PSA criteria (Smith et al, 2005). PSA criteria for defining risk were also discussed at an Oncologic Drugs Advisory Committee (ODAC) meeting in September 2011 addressing potential development pathways for products in patients with nonmetastatic CRPC.
- Additional analyses were performed to confirm that short PSA doubling time was a predictor of risk and to evaluate the treatment effect of denosumab in subsets at higher risk in order to identify subjects who could benefit most from denosumab treatment:
  - Analysis of the placebo arm demonstrated that the risk of developing bone metastases increased continuously as PSA doubling times decreased below 10 months. Compared with the overall study population, time to bone metastases or death was approximately 3 months shorter in subjects with a PSA doubling time ≤ 10 months and 7 months shorter in subjects with a PSA doubling time ≤ 6 months.
  - In the ≤ 10 months PSA doubling time subset, denosumab prolonged median bone metastasis-free survival by 6.0 months compared with placebo with a 16% reduction in risk of developing bone metastases or death.
  - In the ≤ 6 months PSA doubling time subset, denosumab prolonged median bone metastasis-free survival by 7.2 months compared with placebo with a 23% reduction in risk of developing bone metastases or death.
  - Supporting the prespecified analysis for the proportion of subjects with symptomatic bone metastases, the time to symptomatic bone metastasis was longer for subjects who received denosumab compared with those who received placebo, with a 33% reduction in risk.
  - An evaluation of the presence of metastases at multiple sites at the time of detection demonstrated that, despite 4 month intervals between bone scans, approximately 60% of subjects who developed bone metastases had bone metastases at multiple locations. The time to multiple bone metastases was longer for subjects who received denosumab compared with those who received placebo, with a 24% reduction in risk.

Safety of Denosumab

- Pivotal Study 20050147 provides safety data for 720 subjects who received denosumab at 120 mg Q4W compared with 705 subjects who received placebo in the primary blinded treatment period. The median (interquartile range [Q1, Q3]) cumulative exposure was 19.3 (9.3, 30.4) months for denosumab and 18.4 (8.5, 30.4) months for placebo.
- The known risks of hypocalcemia and osteonecrosis of the jaw (ONJ), described in the current approved XGEVA® prescribing information, were also observed in Study 20050147.
  - The subject incidence of adverse events of hypocalcemia was 1.7% in the denosumab group and 0.3% in the placebo group. Grade 3 and 4 low serum calcium values (< 7 mg/dL) occurred in 1.3% of subjects treated with denosumab and 0% of subjects treated with placebo.
  - Events of ONJ occurred in 4.6% of subjects in the denosumab group and 0% in the placebo group. Among these events, 70% were mild to moderate in severity, 30% were managed conservatively with mouth rinses and antibiotics, and 64% had limited local surgical procedures, such as debridement; 2 subjects had bone resection. Resolution occurred in approximately 40% of subjects.
  - When adjusted for duration of exposure, the rates of ONJ were similar across Study 20050147 and the completed SRE trials. The cumulative rate of ONJ at year 1 was approximately 1 event per 100 subject-years, and at years 2 and 3, was approximately 2 events per 100 subject-years.
  - The risks of hypocalcemia and ONJ have been well characterized throughout the clinical development program of denosumab. The XGEVA® prescribing information communicates to healthcare providers appropriate preventive and corrective measures to manage these events.
- Safety results in the subsets of subjects with PSA doubling times ≤ 10 months and ≤ 6 months were consistent with those in the overall population.
- No new safety risks associated with denosumab were identified in the study.

Pharmacovigilance Program

- Known risks of hypocalcemia and ONJ are communicated through product labeling. New potential risks will be evaluated through ongoing pharmacovigilance activities in order to continuously assess denosumab's benefit-risk profile in all approved indications.
- Key proactive pharmacovigilance activities include evaluation of hypocalcemia in a phase 1 study in subjects with severe renal impairment or dialysis, an observational study to evaluate the natural history and resolution of ONJ, and ongoing adjudication for all suspected cases of ONJ.

Conclusions

- The development of bone metastases in patients with nonmetastatic CRPC is associated with significant morbidity that continues until death.
- Despite attempts with the bisphosphonate zoledronic acid (Smith et al, 2005) and the endothelin receptor antagonists atrasentan (Nelson et al, 2008) and zibotentan (AstraZeneca, 2011) to improve clinical outcomes in this patient population, no therapy has been approved specifically for the prevention of bone metastases.

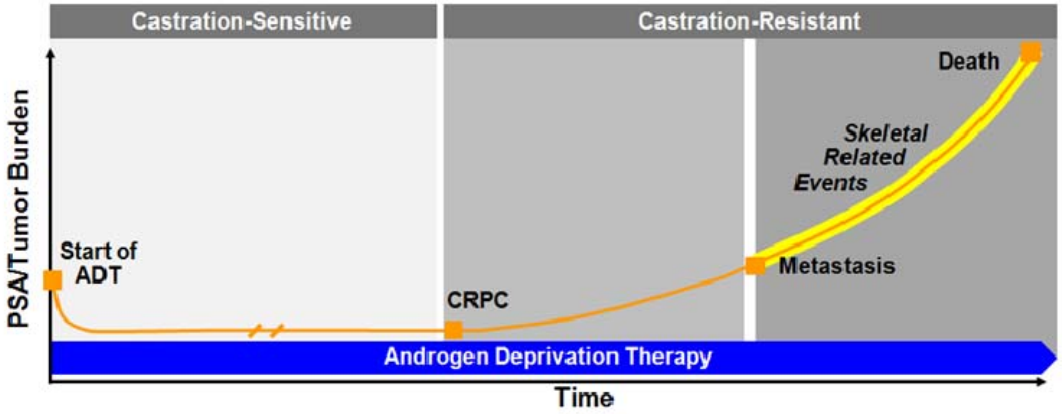
- Denosumab is a RANKL inhibitor that is the first therapy to demonstrate a clinically meaningful benefit in men with nonmetastatic CRPC by preventing or delaying bone metastases.
- Study 20050147 supports the use of PSA doubling time to readily identify high risk patients most likely to benefit from denosumab's ability to delay the development of bone metastases.
- The demonstration of a 4.2 month delay in time to bone metastasis or death in Study 20050147 compared with placebo, together with the demonstration of a 3.6 month delay in time to first SRE in Study 20050103 compared with zoledronic acid provides comprehensive evidence for the activity of denosumab against bone metastases in prostate cancer.
- The risks of denosumab in men with nonmetastatic CRPC as identified in this study are consistent with patients with advanced cancer and bone metastases treated with denosumab and include hypocalcemia and ONJ.
- The efficacy of denosumab in preventing bone metastases is clear and is consistent with the efficacy demonstrated in patients with established bone metastases in preventing SREs. The clinical benefits of preventing bone metastases are most apparent in men at high risk of developing metastases as defined by PSA criteria. These men will almost invariably develop bone metastases and be at risk for SREs. Selection of appropriate high-risk patients for treatment with denosumab should consider the risk of ONJ since this is the most important adverse consequence of inhibition of bone resorption.

3. Nonmetastatic, Castration-resistant Prostate Cancer

3.1 Disease Background

Prostate cancer is diagnosed each year in over 900,000 men worldwide and constitutes the third most common cause of cancer-related death in men in developed countries (Jemal et al, 2011). In the United States, prostate cancer is the leading cancer among men and the second leading cause of cancer death (ACS, 2011 [Cancer Facts & Figures 2011]; Howlader et al [eds], 2010 [SEER]). Within the continuum of prostate cancer, distinct clinical states can be characterized by differences in hormonal and disease status (Saad and Eastham 2010; Scher et al, 2008; Scher and Heller, 2000; Smith, 2009a). These states, which are of varying durations, include a castration-sensitive nonmetastatic phase; a castration-resistant nonmetastatic phase; and a castration-resistant metastatic phase, as illustrated in Figure 1 and described further below.

Figure 1. Disease States in Prostate Cancer



Adapted from Smith MR. Eur Urol Suppl 2009;8:834-838
ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; PSA = prostate-specific antigen

Patients with prostate cancer typically present with localized disease that is sensitive to androgen deprivation. Androgen deprivation therapy (ADT) is used as adjuvant therapy for node positive disease after prostatectomy, adjuvant therapy for locally advanced disease in combination with radiation therapy, primary therapy for locally advanced disease, and salvage therapy for rising PSA after surgery and/or radiation therapy (Bolla et al, 1997; Messing et al, 1999; Sharifi et al, 2005). Following a period of hormone sensitivity on ADT, disease progression occurs, often based only on rising PSA levels and signaling the onset of the nonmetastatic, castration-resistant state. It is

common clinical practice to continue ADT despite evidence of recurrence or progression of prostate cancer (including PSA recurrence) and, as indicated in a national guideline, continued treatment with ADT is recommended because the androgen receptor remains active in the castration-resistant state (National Comprehensive Cancer Network®, 2011).

Once they are considered castration-resistant, patients are at increased risk of developing clinically apparent metastatic disease, particularly to bone (Smith et al, 2005). Indeed, bone metastases develop in up to 90% of patients with metastatic prostate cancer (Bubendorf et al, 2000).

Increased PSA levels and shorter PSA doubling times are significantly associated with shorter time to bone metastasis or death in patients with nonmetastatic CRPC (Smith et al, 2005; Smith et al, 2011a).

Of the approximately 2.4 million men living with a history of prostate cancer in the United States, an estimated 54,000 (2%) have CRPC with a high risk of developing bone metastases (Howlader et al [eds], 2010 [SEER]; data on file, Amgen).

The development of bone metastases is a life-changing event in the natural history of men with castration-resistant nonmetastatic prostate cancer. Bone metastases are irreversible and progressive throughout the remaining period of approximately 2 years of life (Bhandari et al, 2005; de Bono et al, 2010a, 2010b; Kantoff et al, 2010; Tannock et al, 2004). Bone metastases can result in incapacitating complications, which are represented by SREs including pathologic fractures that may impair ambulation; radiation therapy to bone and bone surgery to prevent or treat pathologic fractures or manage pain; and spinal cord compressions that can result in numbness or weakness, urinary or fecal incontinence, and paralysis (Coleman, 2006). For many patients, these complications result in loss of function and independence, together with reduced quality of life (Coleman, 2006; Harris et al, 2009; Mercadante 1997). At this stage, men also have to confront initiation of a cascade of systemic treatments for metastatic disease, because additional hormonal manipulations, chemotherapy, and immunotherapy are introduced (de Bono et al, 2010a, 2010b; Kantoff et al, 2010; Tannock et al, 2004).

3.2 Unmet Medical Need

Although several treatment options are available for men with metastatic CRPC, there are no approved treatments directed either at prostate cancer or at the prevention of bone metastases for those patients who have CRPC but have not yet developed

metastatic disease. In metastatic CRPC, more patients who received mitoxantrone plus prednisone (29%) compared with prednisone (12%) alone experienced improved quality of life based on primary pain response and there was an improvement in median duration of primary pain response by 5.5 months (NOVANTRONE®, 2002).

Since 2004, 4 other agents have been approved that prolong survival in metastatic CRPC: docetaxel and sipuleucel-T prolonged median overall survival by 2.4 to 4.1 months, respectively (Tannock et al, 2004; Kantoff et al, 2010). In men with metastatic CRPC and disease progression after docetaxel, cabazitaxel and abiraterone prolonged median overall survival by 2.4 to 3.9 months, respectively (de Bono et al, 2010a; de Bono et al, 2010b).

Systemic treatments for metastatic disease also include the use of bone-targeted therapies, including denosumab (XGEVA®, 2010 in Appendix 1) or zoledronic acid (Zometa®, 2011) to prevent skeletal complications (ie, SREs) (National Comprehensive Cancer Network®, 2011). Study 20050103 in men with CRPC and bone metastases comprised one of the 3 pivotal phase 3 studies that supported approval of XGEVA® and demonstrated that denosumab prolonged median time to first on-study SRE by 3.6 months compared with zoledronic acid.

For patients who have CRPC but have not yet developed metastatic disease, multiple preventive attempts with bone-targeted agents have been undertaken because bone metastases constitute the most frequent metastatic manifestation of advanced prostate cancer (Bubendorf et al, 2000). These include the bisphosphonates clodronate (in hormone-sensitive prostate cancer; Mason et al, 2007) and zoledronic acid (Smith et al, 2005), as well as the endothelin receptor antagonist atrasentan (Nelson et al, 2008) in CRPC. A study with another endothelin receptor antagonist, zibotentan, in patients with CRPC without bone metastases has recently been terminated for lack of efficacy (AstraZeneca, 2011). None of these agents have demonstrated significant efficacy in preventing or delaying bone metastases and no therapy is approved in this setting.

The need for development of new therapies in patients with nonmetastatic CRPC was recently discussed at an ODAC convened on 14 September 2011. The patient population with nonmetastatic CRPC was acknowledged to be at risk of developing bone metastases. The committee discussed the value of enrolling subjects at high risk of bone metastases, particularly those with short PSA doubling times. Prevention or delay of bone metastases leading to prolongation of bone metastasis-free survival was considered a clinically important outcome by several ODAC members, with varying

perspectives on the magnitude of treatment effect compared with placebo necessary to demonstrate a clinically meaningful benefit. Study designs and efficacy endpoints to support an indication in this population were discussed. Among other considerations, a placebo-controlled study design for an unlicensed product and an early intervention versus delayed intervention study design for a licensed product with already established benefit in patients with metastatic disease were considered appropriate.

The lack of available treatments to prevent metastases in patients with CRPC, coupled with the recent recognition of the need to develop new therapies in this population, underscores the unmet medical need.

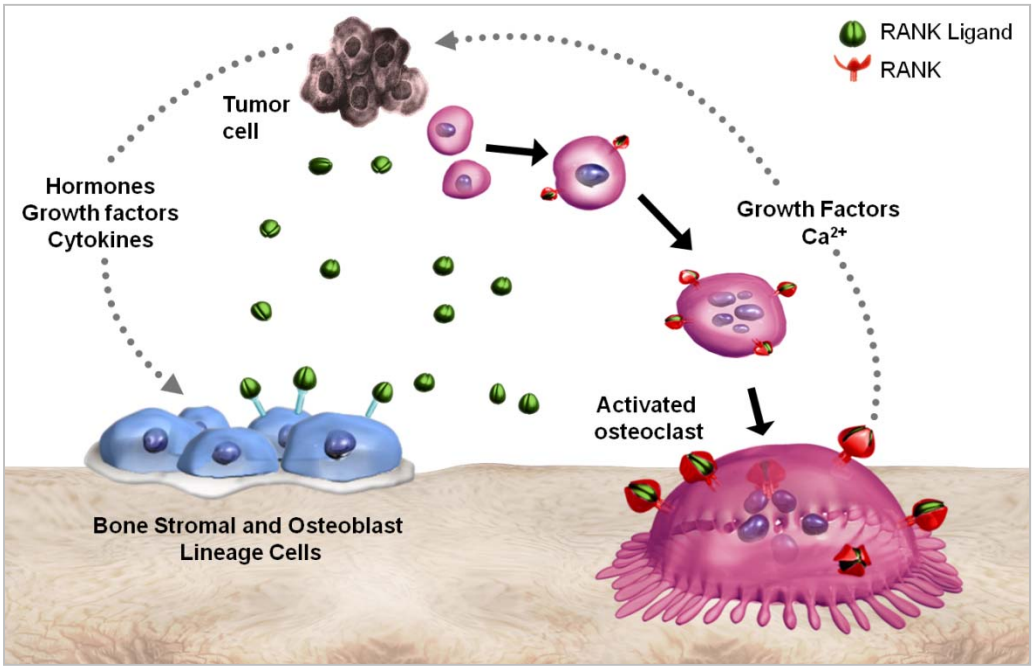
4. Denosumab

4.1 Role of RANK Ligand in the Development of Bone Metastases

RANK ligand binds to RANK on osteoclasts or osteoclast precursors and is an essential factor in the formation, activation, and survival of osteoclasts, which is the sole cell type responsible for bone resorption (Burgess et al, 1999; Lacey et al, 1998; Yasuda et al, 1998).

Figure 2 depicts the vicious cycle hypothesis of bone metastasis establishment and progression, which is dependent upon a reciprocal interaction between tumor cells and bone (reviewed in Roodman and Dougall, 2008). Growth factors and cytokines released from cancer cells in bone cause a local increase in RANKL levels that drives osteoclast activity and bone resorption (Mundy, 2002; Yoneda and Hiraga, 2005). Osteoclast-mediated bone resorption, in turn, appears to release growth factors from the bone that create an environment that promotes tumor cell homing, survival, and proliferation in the bone, resulting in the establishment and progression of metastases. Experimental inhibition of osteoclasts by inhibition of RANKL not only prevents tumor-induced osteolysis and decreases progression of established skeletal tumors, but also significantly delays the de novo formation and establishment of bone metastases in rodent models of bone metastasis that represent osteolytic, osteoblastic, and mixed bone lesions (Canon et al, 2008a; Canon et al, 2008b; Yonou et al, 2003; Zhang et al, 2003; Zhang et al, 2001). One of these studies assessed early treatment with a RANKL inhibitor in a mouse model of prostate cancer bone metastasis, in which the establishment of skeletal tumors was completely blocked (Zhang et al, 2001), which is consistent with the hypothesis that osteoclastogenesis and active bone turnover are critical events in the early steps of outgrowth of skeletal micrometastases. Additionally, RANKL inhibition effectively prevents bone metastases in androgen-depleted (hypogonadal) mice (Padalecki et al, 2007).

Figure 2. The 'Vicious Cycle' Hypothesis of Bone Metastasis Establishment and Progression

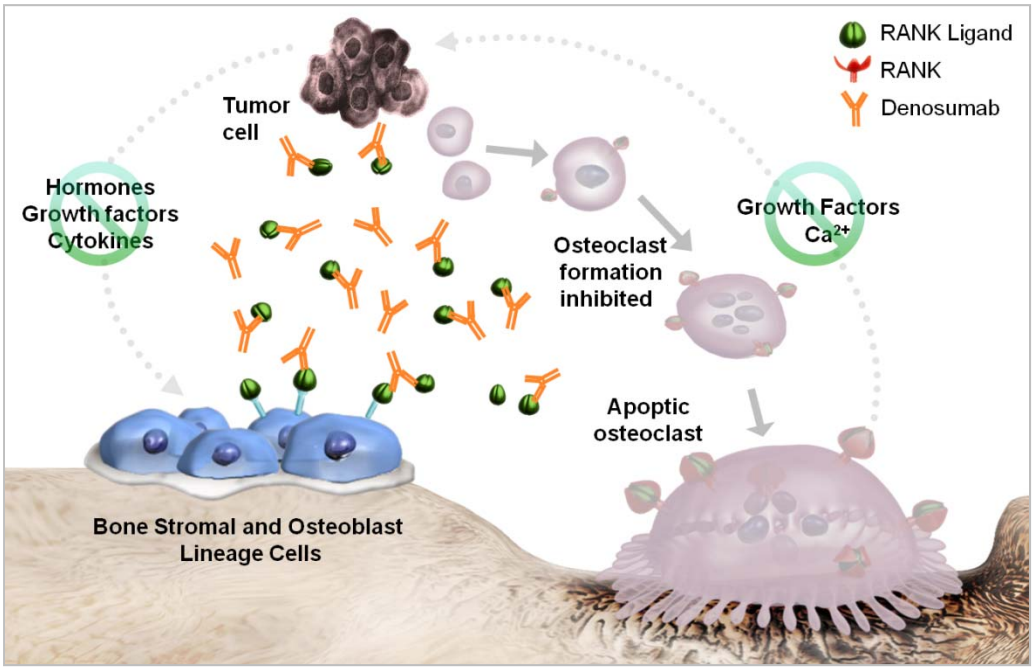


Source: Adapted from Roodman and Dougall, 2008.

4.2 Mechanism of Action of Denosumab

Denosumab is a fully human monoclonal IgG2 antibody to RANKL that binds with high affinity (Kd 3 x 10^{-12} M) and specificity to the soluble and cell membrane-bound forms of human RANKL. Denosumab binding to RANKL prevents RANK activation and inhibits the formation, activation, and survival of osteoclasts (Figure 3). As a result of its unique and specific mechanism of action, denosumab is effective for prevention of SREs in men with metastatic CRPC, and its use in men with CRPC to prevent or delay bone metastases is presented in this document.

Figure 3. Mechanism of Action of Denosumab



Source: Adapted from Roodman and Dougall, 2008.

4.3 Clinical Studies with Denosumab in Prostate Cancer

4.3.1 Phases of Prostate Cancer

A comprehensive development program has been conducted to examine the efficacy and safety of denosumab across the continuum of prostate cancer, including studies in the castration-sensitive nonmetastatic phase (Study 20040138), castration-resistant nonmetastatic phase (Study 20050147), and castration-resistant metastatic phase (Study 20050103) (Table 1).

For men with CRPC, the objectives of the clinical program were to evaluate if denosumab could prevent the development of clinically evident bone metastases (Study 20050147), and if denosumab could prevent the debilitating clinical consequences caused by already established and clinically evident bone metastases, collectively referred to as SREs (Study 20050103). Patients in Study 20050147 were selected using criteria that conferred a high risk for development of bone metastases, thus reflecting a stage of disease that immediately preceded the population studied in Study 20050103. These two studies were initiated in 2006 and were conducted in parallel and complement each other by providing comprehensive evidence for the activity of denosumab in preventing the evolution of bone metastases from absent or undetectable micrometastases to clinically evident metastases and in preventing the clinical sequelae associated with established bone metastases, including SREs.

Importantly, radiographically confirmed bone metastases were a key component of the primary endpoint in Study 20050147 and were the key study entry criterion in Study 20050103.

Results from Study 20050103 have previously been reported and comprised one of the 3 studies that supported the approval of denosumab 120 mg Q4W (under the proprietary name XGEVA®) for the prevention of SREs in patients with bone metastases from solid tumors. The results of Study 20050103 demonstrate clinically relevant delays in the time to first SRE, reductions in the overall burden of SREs, and superior efficacy of denosumab (120 mg Q4W) compared with zoledronic acid (4 mg Q4W) in subjects with CRPC and bone metastases. The hazard ratio for the time to first on-study SRE was 0.82 (95% CI: 0.71, 0.95); p = 0.0085 (unadjusted and adjusted) and the rate ratio for the time to first and subsequent on-study SRE was 0.82 (95% CI: 0.71, 0.94); p = 0.0044 (unadjusted) and 0.0085 (adjusted).

In Study 20050147, the ability of denosumab to demonstrate a clinically meaningful benefit in men with nonmetastatic CRPC by preventing or delaying bone metastases was evaluated. Positive results from this study would support intervening earlier in the prostate cancer treatment continuum to prevent the significant morbidity, including SREs associated with bone metastases.

Study 20040138 was also conducted to evaluate the ability of denosumab to increase bone mineral density and reduce fracture in men with castration-sensitive nonmetastatic prostate cancer. Results from this study showed that denosumab increased bone mineral density (BMD) at all anatomic sites in men undergoing ADT treated with denosumab (60 mg Q6M), compared with placebo. Denosumab increased BMD from baseline by 6.8% and 3.2% at the lumbar spine and total hip, respectively. The difference from placebo was 7.9% and 5.7%, respectively. Denosumab also significantly decreased the subject incidence of new vertebral fractures by 62% over the 36-month treatment period (adjusted p = 0.0125). These results supported approval of denosumab (under the proprietary name of Prolia®) at a different dose and schedule (60 mg SC Q6M) as treatment to increase bone mass in men at high risk for fracture receiving ADT for nonmetastatic prostate cancer.

4.3.2 Pivotal Study 20050147

The comprehensive clinical program for denosumab was designed with consideration of the applicable guidelines for clinical study design and report preparation, assessment of safety and efficacy, selection of endpoints, and statistical principles. Clinical studies

were conducted under Good Clinical Practices as described in International Conference on Harmonisation (ICH) E6 (ICH, 1996), under the principles of the Declaration of Helsinki, and in accordance with local and regional regulations.

Study 20050147 included study centers in Europe, North America, Latin America, South Africa, Australia, New Zealand, and India. Health authority input on the overall development program and the design of the study was provided in response to clinical trial applications in several regions and through formal regulatory interactions in the United States, Europe, and Canada prior to study initiation.

In the United States, a formal pre-phase 3 meeting between Amgen and FDA was held on 20 September 2005 to discuss the design of the study, Study 20050147. Outcomes of note from this meeting were agreements between the Agency and Amgen that the study design and statistical approach of Study 20050147, including the use of bone metastasis-free survival as the primary endpoint, would be acceptable to support an indication in this patient population. Bone metastasis-free survival represents the development of centrally confirmed bone metastases, either symptomatic or asymptomatic, or death, whichever comes first and is a measure of the time that patients lived without progressing to bone metastases. The Agency also stated that overall survival, patterns of metastases, and the development of symptomatic metastases would be important review issues and that results from Studies 20040138 and 20050103 should be consistent with the findings of Study 20050147.

On 05 April 2011, a formal pre-sBLA meeting between Amgen and FDA was held, and the Agency accepted that the clinical data from Study 20050147, supported by data from other randomized trials conducted in patients with prostate cancer, including Studies 20050103 and 20040138, were adequate to support an sBLA submission for the proposed prostate cancer indication.

Of note, the study design of completed Study 20050147 is also consistent with one of the approaches presented at the recent 14 September 2011 ODAC meeting for new studies in men with nonmetastatic CRPC.

4.4 Clinical Studies of Denosumab in Other Cancer Patients

Data from 2 other pivotal studies of denosumab in subjects with cancer were provided in the sBLA for comparison with Study 20050147 where appropriate (Table 2). These include the other 2 pivotal phase 3 studies that supported the approval of denosumab (XGEVA®) to prevent SREs in patients with bone metastases from solid tumors

(20050136 and 20050244). In these studies and in Study 20050103 described above, the same dose and schedule of denosumab was used as in Study 20050147 (120 mg SC Q4W). The 3 SRE phase 3 studies included the well-characterized active comparator zoledronic acid (4 mg administered intravenously Q4W). The denosumab efficacy and safety results from the 3 SRE phase 3 studies using a dose of 120 mg Q4W are described in the approved XGEVA® prescribing information (XGEVA®, 2010 in Appendix 1).

Table 1. Clinical Studies With Denosumab in Prostate Cancer

Protocol Number	Study Design	Population	Primary Objective	Publications
20050147	Phase 3, randomized, double-blind, placebo-controlled Denosumab: 120 mg SC Q4W Placebo: SC Q4W Event driven: double-blind treatment phase with primary analysis phase determined by the anticipated date on which ~660 subjects developed a bone metastasis or died, followed by a 3-year open-label extension phase[a]	1432 (1425 dosed; 716 denosumab, 709 placebo as randomized) men with histologically confirmed prostate cancer Castration-resistant prostate cancer demonstrated during continuous ADT/post-orchiectomy evidenced by a rising PSA[b] High risk for bone metastases; no previous/current radiographic evidence of bone metastases Serum testosterone level of < 50 ng/dL due to either surgical or chemical castration ECOG status of 0 or 1 No prior or current IV bisphosphonate administration No osteonecrosis/osteomyelitis of the jaw Age: ≥18 yr	To compare the treatment effect of denosumab with placebo on prolonging bone metastasis-free survival in men with hormone-refractory (androgen-independent) prostate cancer who have no bone metastases at baseline	Smith et al, 2011b

ADT = androgen-deprivation therapy; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; PSA = prostate-specific antigen; Q4W = once every 4 weeks; SC = subcutaneously

[a] or until subject develops a bone metastasis or obtains access to commercially available product in this setting, whichever comes first

[b] defined as 3 consecutive determinations, taken at least 2 weeks apart from one another. The second and third measurements must be ≥ 1.0 ng/mL

Table 1. Clinical Studies With Denosumab in Prostate Cancer

Number	Study Design	Population	Primary Objective	Publications
20050103	Phase 3, randomized, double-blind, active-controlled Denosumab: 120 mg SC and zoledronic acid placebo IV Q4W Active control: zoledronic acid 4 mg IV and denosumab placebo SC Q4W Event-driven, double-blind treatment phase with primary analysis phase determined by the anticipated date on which ~745 subjects experience an initial on study SRE, followed by a 2-year survival follow-up period or a 2-year open-label extension phase[a]	1901 (1888 dosed; 942 denosumab, 946 zoledronic acid, as randomized) men with histologically confirmed prostate cancer Current or prior radiographic (ie, x-ray, CT, or MRI) evidence of at least 1 bone metastasis Documented failure of at least 1 hormonal therapy as evidenced by a rising PSA[b] Serum testosterone level of < 50 ng/dL due to either surgical or chemical castration Age: ≥ 18 yr	To determine if denosumab is non-inferior to zoledronic acid with respect to the first on-study occurrence of an SRE	Fizazi et al, 2011
20040138	Phase 3, randomized, double-blind, placebo-controlled Denosumab: 60 mg SC Q6M (6 doses) Placebo: 60 mg SC Q6M (6 doses) 36-month double-blind treatment period + 24-month safety follow-up	1468 (1456 dosed; 726 denosumab, 730 placebo, as randomized) men with nonmetastatic prostate cancer receiving ADT BMD T-score < -4.0 at lumbar spine, total hip, or femoral neck excluded For those < 70 yr of age (but not those ≥ 70 yr): evidence of bone loss (ie, history of osteoporotic fracture or BMD T-score < -1.0 at the lumbar spine, total hip, or femoral neck) Age: ≥ 18 yr	To determine the treatment effect of denosumab compared with placebo on lumbar spine BMD at month 24 in men with nonmetastatic prostate cancer undergoing ADT	Smith et al, 2009b

ADT: androgen deprivation therapy; BMD = bone mineral density; CT = computed tomography; IV = intravenously; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; Q4W = once every 4 weeks; Q6M = every 6 months; SC = subcutaneously; SRE = skeletal-related event

[a] or until denosumab is commercially available, whichever comes first

[b] defined as 3 consecutive determinations, taken at least 2 weeks apart from one another. .The third measurement must be ≥ 0.4 ng/mL and be taken within 8 weeks prior to randomization.

Table 2. Other Clinical Studies of Denosumab in Advanced Cancer

Protocol Number	Study Design	Population	Primary Objective	Publications
20050136	Phase 3, randomized, double-blind, active-controlled Denosumab: 120 mg SC and zoledronic acid placebo IV Q4W Active control: zoledronic acid 4 mg IV and denosumab placebo SC Q4W Event-driven, double-blind treatment phase with primary analysis phase determined by the anticipated date on which ~745 subjects experience an initial on-study SRE, followed by a 2-year survival follow-up period or a 2-year open-label extension phase[a]	2046 (2033 dosed; 1019 denosumab, 1014 zoledronic acid, as randomized) women or men with histologically or cytologically confirmed breast adenocarcinoma Current or prior radiographic (ie, x-ray, CT, or MRI) evidence of at least 1 bone metastasis Age: ≥ 18 yr	To determine if denosumab is non-inferior to zoledronic acid with respect to the first on-study occurrence of an SRE	Stopeck et al, 2010
20050244	Phase 3, randomized, double-blind, active-controlled Denosumab: 120 mg SC and zoledronic acid placebo IV Q4W Active control: zoledronic acid 4 mg IV and denosumab placebo SC Q4W Event-driven, double-blind treatment phase with primary analysis phase determined by the anticipated date on which ~745 subjects experience an initial on-study SRE, followed by a 2-year survival follow-up period	1776 (1756 dosed; 878 denosumab, 878 zoledronic acid, as randomized) men or women with histologically or cytologically confirmed advanced cancers including solid tumors (except breast and prostate cancer), multiple myeloma, and lymphoma Current or prior radiographic (ie, x-ray, CT, or MRI) evidence of at least 1 bone metastasis (or lytic bone lesion from multiple myeloma) Age: ≥ 18 yr	To determine if denosumab is non-inferior to zoledronic acid with respect to the first on-study occurrence of an SRE	Henry et al, 2011

ADT: androgen-deprivation therapy; BMD = bone mineral density; CT = computed tomography; IV = intravenously; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; Q4W = once every 4 weeks; Q6M = every 6 months; SC = subcutaneously; SRE = skeletal-related event

[a] or until denosumab is commercially available, whichever comes first

[b] defined as 3 consecutive determinations, taken at least 2 weeks apart from one another. The third measurement must be ≥ 0.4 ng/mL and be taken within 8 weeks prior to randomization.

4.5 Denosumab Indications

4.5.1 Approved Indications

Denosumab has been approved in the United States under the proprietary name XGEVA® (denosumab 120 mg Q4W SC) for the prevention of SREs in patients with bone metastases from solid tumors. This approval was based on results from 3 phase 3 studies, including 1 in men with prostate cancer and bone metastases. Results demonstrated that denosumab was superior to the active comparator, zoledronic acid, for the prevention of SREs.

Denosumab has also been approved in the United States under the proprietary name Prolia® (denosumab 60 mg Q6M SC) for treatment of postmenopausal women with osteoporosis at high risk of fracture, treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer, and treatment of bone loss in men receiving ADT for nonmetastatic prostate cancer. In these men, denosumab also reduced the incidence of vertebral fractures.

4.5.2 Proposed Indication

Study 20050147 was conducted in a population of men with CRPC at high risk for development of bone metastases. In this study, high risk was defined as having a PSA value ≥ 8.0 ng/mL and/or a PSA doubling time ≤ 10.0 months. Based on the positive results from the overall population in this trial, Amgen has proposed a new indication in the recently submitted sBLA, which is as follows:

> XGEVA® is indicated for the treatment of men with castration-resistant prostate cancer at high risk of developing bone metastases. XGEVA® prolongs bone metastasis-free survival by reducing the risk of developing bone metastases.

4.5.3 Other Oncology Indications Under Investigation

Prior agreements between FDA and Amgen on the study design and statistical approach of Study 20050147 and on other randomized cancer trials in support of an sBLA submission for the proposed prostate cancer indication are described in Section 4.3. Denosumab is also being evaluated as adjuvant treatment for women with early-stage breast cancer at high risk of disease recurrence receiving standard-of-care adjuvant/neoadjuvant cancer therapy, for the prevention of SREs in patients with multiple myeloma, for the treatment of giant cell tumor of bone, and for the treatment of hypercalcemia of malignancy.

5. Dosing Regimen in Men With Castration-resistant Prostate Cancer at High Risk of Developing Bone Metastases

The dosing regimen for denosumab used in Study 20050147 was 120 mg SC Q4W, which is the dosing regimen that was approved for denosumab for the prevention of SREs in patients with bone metastases from solid tumors (XGEVA®, 2010 in Appendix 1). Amgen considers it appropriate to target the same steady-state serum denosumab concentrations in patients with CRPC at high risk of developing bone metastases as in patients with established bone metastases from solid tumors. Despite different clinical endpoints in these patient populations (ie, bone metastasis-free survival vs prevention of SREs), the treatment intent is the same: to achieve maximal suppression of bone resorption in the highest proportion of patients and to maintain this level of suppression over the entire dose interval.

The population pharmacokinetic/pharmacodynamic analysis conducted for XGEVA® provided robust support in justifying the 120-mg Q4W dosing regimen in patients with advanced cancer. Collectively, the modeling and simulations illustrated 4 key properties of this dose regimen, assessed using levels of urinary N-telopeptide corrected for urine creatinine (uNTx/Cr), a marker of bone resorption: (a) 120-mg Q4W dosing resulted in a higher proportion of subjects with uNTx/Cr levels < 50 nM bone collagen equivalent (BCE)/mM relative to 30-mg Q4W dosing, (b) Q4W dosing resulted in a greater proportion of subjects with uNTx/Cr suppression > 90% across all doses relative to once every 12 weeks dosing, (c) 120 mg was the lowest Q4W dose producing the maximal proportion of subjects with uNTx/Cr suppression > 90%, and (d) 120-mg Q4W dosing resulted in a substantial reduction in the absolute variability in uNTx/Cr as compared with lower denosumab doses.

Pharmacokinetic results from Study 20050147 indicate that after 120-mg Q4W dosing, exposures based on trough serum denosumab concentrations increased approximately 2-fold up to week 25, by which time steady-state was attained. Thereafter, trough serum denosumab concentrations did not change up to week 73, consistent with a lack of change in pharmacokinetics with time and upon multiple dosing. Mean trough serum denosumab concentrations in the study (range of 6750 to 15,200 ng/mL) were very similar to those observed in men with advanced prostate cancer and bone metastases in Study 20050103 (7190 to 17,700 ng/mL). Also, the mean trough uNTx/Cr level at week 25 (10.4 nM BCE/mM of creatinine) was very similar to that at week 13 in Study 20050103 (12.8 nM BCE/mM of creatinine). Similarity in denosumab pharmacokinetics

and pharmacodynamics between subjects in Studies 20050147 and 20050103 supports the use of the same dosing regimen in both study populations.

Additionally, results from Study 20050147 have demonstrated the efficacy (Section 6) and safety (Section 7) of the proposed 120-mg SC Q4W dosing regimen. The efficacy observed in the study confirms that selecting a dosing regimen producing maximal suppression of uNTx/Cr was an appropriate strategy for dose selection. Furthermore, denosumab administered at a dose of 120 mg SC Q4W had an acceptable safety profile in Study 20050147 and the pivotal phase 3 SRE studies. Therefore, 120 mg SC Q4W is proposed as the dosing regimen for the new indication.

6. Efficacy of Denosumab for the Treatment of Men With Castration-resistant Prostate Cancer at High Risk of Developing Bone Metastases

6.1 Study 20050147 Design and Efficacy Endpoints

As discussed in Section 4.3.2, Study 20050147 was an international, phase 3, randomized, double-blind, placebo-controlled study. The eligibility criteria for this study required enrollment of men who had castration serum testosterone levels due to chemical or surgical castration (< 50 ng/mL) but had evidence of castration-resistance (rising PSA despite castration serum testosterone levels). Men were also required to be at high risk for the development of bone metastases, requiring a PSA value ≥ 8.0 ng/mL (obtained no more than 3 months before randomization) or a PSA doubling time ≤ 10.0 months. These criteria were selected because elevated PSA and short PSA doubling times have been associated with increased risk of developing bone metastases or death (Smith et al, 2005). Eligible subjects were randomly assigned (1:1) to receive either denosumab administered at a dose of 120 mg SC Q4W or placebo administered SC Q4W. Randomization was stratified based on PSA criteria (PSA level ≥ 8.0 ng/mL and PSA doubling time ≤ 10.0 months [yes/no] and previous or current chemotherapy for prostate cancer [yes/no]).

Subjects were advised to take daily oral supplements of calcium (≥ 500 mg) and vitamin D (≥ 400 IU) throughout the study unless hypercalcemia (albumin-adjusted serum calcium > 2.9 mmol/L [> 11.5 mg/dL] or ionized calcium > 1.5 mmol/L) developed on study.

During the primary blinded treatment phase of the study, subjects received investigational product until approximately 660 subjects were to have developed bone metastases or died (primary analysis). Subjects developing bone metastases discontinued investigational product and study because approved bone-targeted therapy was available to prevent SREs. These subjects were then followed for overall survival. Assuming the hazard ratio of denosumab versus placebo was 0.8, 660 study events provided approximately 80% power at a significance level of 0.025 using a 1-sided maximum likelihood test. The primary efficacy and safety analyses were performed at the end of the primary blinded treatment phase, and the results are the basis for the overall efficacy and safety conclusions for the study. Subjects continued to receive blinded investigational product for a period beyond the primary analysis cut-off date until the primary efficacy and safety analysis were completed (extended blinded treatment phase). An exploratory analysis was also performed at the end of the entire blinded

treatment phase, which also included results from the extended blinded treatment phase.

Once the primary analysis was completed, denosumab was determined to have a positive benefit-risk profile compared with placebo, and all subjects who completed blinded treatment were offered open-label denosumab 120 mg SC to continue treatment for up to 3 years. This open-label treatment period is ongoing. Subjects who discontinued investigational product in either the double-blind or open-label phase are being followed for survival. For these subjects, survival data are collected by clinic visit or telephone contact every 6 months for up to 3 years after the last dose of blinded investigational product.

Key efficacy endpoints are listed in Table 3, and details of planned statistical analyses are provided in Section 6.2.

The intent of Study 20050147 was to confirm that denosumab could prevent bone metastases, a clinically important outcome, based on its bone-targeted mechanism of action; therefore, the focus of design and conduct of the study was on the detection of bone metastases. The primary efficacy endpoint was bone metastasis-free survival, as determined by time to first occurrence of bone metastasis (symptomatic or asymptomatic at detection) or on-study death from any cause, whichever occurred first. Death on study prior to the development of bone metastases was included in the primary endpoint in order to account for any potential imbalance in this critical outcome.

The evaluation of bone metastases was performed by a radiology facility using a centralized rigorous and reproducible process. All potential bone metastases, whether those evaluated for eligibility or those documented on study, were analyzed by central review with 2 independent readers, using the same process. A third reader adjudicated if the initial review for the presence of bone metastases was discordant. All readers were blinded to treatment assignment. To determine eligibility for study entry, the central imaging laboratory excluded the presence of bone metastases using bone scans and skeletal survey. If any abnormality was seen on bone scan, additional x-ray, computed tomography (CT), or magnetic resonance imaging (MRI) scans were required to establish evidence of a benign cause for the lesion in order for the subject to be eligible. During the treatment phase, bone scans were scheduled every 4 months and a skeletal survey every year. If the bone scan identified any change from baseline, additional x-ray, CT, or MRI scans were obtained and were used by the central reader to confirm or exclude the presence of bone metastases. Once there was central confirmation, the

investigator recorded whether there were symptoms associated with the bone metastases.

The secondary efficacy endpoints included time to first bone metastasis (either symptomatic or asymptomatic) excluding death and overall survival time. Of note, unlike the primary endpoint, this secondary survival endpoint included both on-study deaths and deaths during follow-up.

The incidence of symptomatic bone metastases was assessed as an exploratory endpoint.

Other exploratory endpoints in this study included prostate cancer progression-free survival and change in PSA level. Prostate cancer progression-free survival was defined as the time to centrally determined bone metastases, investigator-determined disease progression outside of bone, or on-study death from any cause, whichever came first. Subjects were required to visit the clinic once a month for study purposes in addition to receiving standard-of-care disease evaluation and treatment of the underlying cancer. Evaluations of PSA were performed every 2 months to compare changes between treatment groups.

Fractures were evaluated in exploratory fashion because denosumab has demonstrated anti-fracture efficacy in bone-loss settings.

Patient-reported outcomes (PRO) included exploratory assessments of pain with the Brief Pain Inventory Short Form (BPI-SF) and health-related quality of life (HRQOL) with the Functional Assessment of Cancer Therapy-General (FACT-G). Because subjects with central reader-confirmed bone metastases discontinued both investigational product and study and were only followed for survival, the ability to determine the impact of bone metastases on PRO endpoints was limited.

Table 3. Key Efficacy and Selected Exploratory Endpoints

Level of Endpoint	Endpoint
Primary	Bone metastasis-free survival determined by the time to first occurrence of bone metastasis (either symptomatic or asymptomatic) or death from any cause
Secondary	Time to first bone metastasis (either symptomatic or asymptomatic) excluding death
	Overall survival time
Selected Exploratory	Prostate cancer progression-free survival
	Subject incidence of symptomatic bone metastasis
	Subject incidence of vertebral fracture
	Time to first nonvertebral fracture
	PSA (recorded value, percent change, and change from baseline)
	BPI-SF
	"Worst" pain

BPI-SF = Brief Pain Inventory Short Form; PSA = prostate-specific antigen

6.2 Study 20050147 Statistical Considerations

Pre-specification of Analysis

The statistical analysis plan documenting the analyses for all endpoints was finalized before locking the clinical study database and unblinding the treatment assignments. Analyses were executed per the statistical analysis plan, and any analysis that was not prespecified in the statistical analysis plan is considered post hoc and noted as such in this document.

Intention-to-treat Principle

Amgen designed, conducted, and analyzed data following the intention-to-treat principle.

The protocol specified that subjects were to be followed up regardless of whether or not they remained on investigational product or received alternate therapy during the course of study. Investigators were asked to encourage the subjects to continue to participate in study procedures. As long as a subject did not completely withdraw consent from the study, investigators continued making the protocol-specified assessments. All available data were used in the analyses, regardless of compliance to therapy or treatment with alternate therapies.

Analyses of the primary and secondary endpoints of bone metastasis-free survival, time to bone metastasis, and overall survival endpoints included all randomized subjects (full analysis set). The following censoring rules were applied for these endpoints:

- For bone metastasis-free survival, if a subject did not experience a bone metastasis or on-study death, the subject was censored at the last on-study contact date (prior to the survival follow-up phase) or the primary analysis data cutoff date, whichever came first.
- For time to first bone metastasis, if a subject did not experience a bone metastasis, the subject was censored at the last on-study bone assessment date or the primary analysis data cutoff date, whichever came first.
- For overall survival, if a subject did not die, the subject was censored at the last contact date or the primary analysis data cutoff date, whichever came first.

Analyses of exploratory time-to-event endpoints were based on the full analysis set. For these endpoints, if a subject did not experience on-study events, the subject was censored at the last on-study contact date or the primary analysis data cutoff date, whichever came first. For change from baseline in PSA, all subjects in the full analysis set with an observed value at the time of interest were used in the analyses. Analyses of PRO endpoints included all subjects who were randomized and had ≥ 1 postbaseline PRO assessment.

Analysis Methods

Subjects were accrued into the study over a period of time and were followed to a single primary analysis data cutoff date (ie, the date when approximately 660 subjects were anticipated to have developed bone metastases or died). Consequently, this study was designed such that the duration of follow-up for each individual subject could vary. Therefore, the most appropriate and efficient statistical analysis approach using time-to-event analyses was employed for the primary and secondary endpoints.

A proportional hazards model (Cox, 1972) with treatment groups as the independent variable and stratified by factors used to balance randomization was used to compare the primary endpoint of bone metastasis-free survival and secondary endpoints of time to first bone metastasis and overall survival between the 2 treatment groups. Kaplan-Meier estimates were also calculated.

The analyses of the primary and secondary endpoints were conducted hierarchically. The secondary endpoints were only to be tested when the null hypothesis of the primary endpoint was rejected. If superiority of denosumab over placebo for bone metastasis-free survival was established, the secondary endpoint of time to first bone metastasis

was tested. If superiority of denosumab over placebo for time to first bone metastasis also was established, the secondary endpoint of overall survival was tested.

The subject incidence of symptomatic bone metastases at detection also was calculated using the full analysis set in a prespecified exploratory analysis. Additionally, a post hoc analysis of the time to symptomatic bone metastasis was performed using statistical approaches similar to that for the primary endpoint.

Post hoc analysis of time to multiple bone metastases (an event of bone metastasis at > 1 body site) was performed in the same fashion. The following censoring rules were applied:

- For time to multiple bone metastases at detection, subjects who had single-site bone metastasis were censored at their bone metastasis date; subjects who did not have any bone metastases were censored at last image date.

The exploratory endpoint of prostate cancer progression-free survival was analyzed using the Kaplan-Meier method and a stratified and covariate-adjusted Cox proportional hazards model (Cox, 1972). Descriptive statistics were used to summarize changes from baseline in PSA values.

Prostate-specific antigen doubling time as a tool for predicting risk for progression was highlighted at the September 2011 ODAC meeting. As one of the eligibility criteria for entry on this study was a PSA doubling time ≤ 10 months, post hoc analyses of the primary, secondary, and key exploratory endpoints also were performed in this subset of subjects, which includes approximately 80% of subjects enrolled in the study. Based on data indicating that men with a PSA doubling time of ≤ 6.3 months are in the top tertile of risk with a median bone metastasis-free survival of less than 1.5 years (Smith et al, 2005), similar analyses in the subgroup of subjects with a PSA doubling time ≤ 6 months (approximately 60% of the patients enrolled), were also performed.

The subject incidence of vertebral fracture was analyzed using a logistic regression model using the subset of subjects who had a baseline and ≥ 1 postbaseline evaluation of vertebral fracture at or prior to the time point under consideration. The time to fracture endpoint was analyzed using the Kaplan-Meier method and a stratified Cox proportional hazards model (Cox, 1972) using the full analysis set.

Brief Pain Inventory Short Form worst pain time-to-event endpoints were estimated using the Kaplan-Meier method and a stratified and covariate-adjusted Cox proportional

hazards model (Cox, 1972). The BPI-SF worst pain subject incidence endpoints were summarized by visit up to the visit when ≥ 30% of subjects had discontinued the study due to death, disease progression, or consent withdrawn.

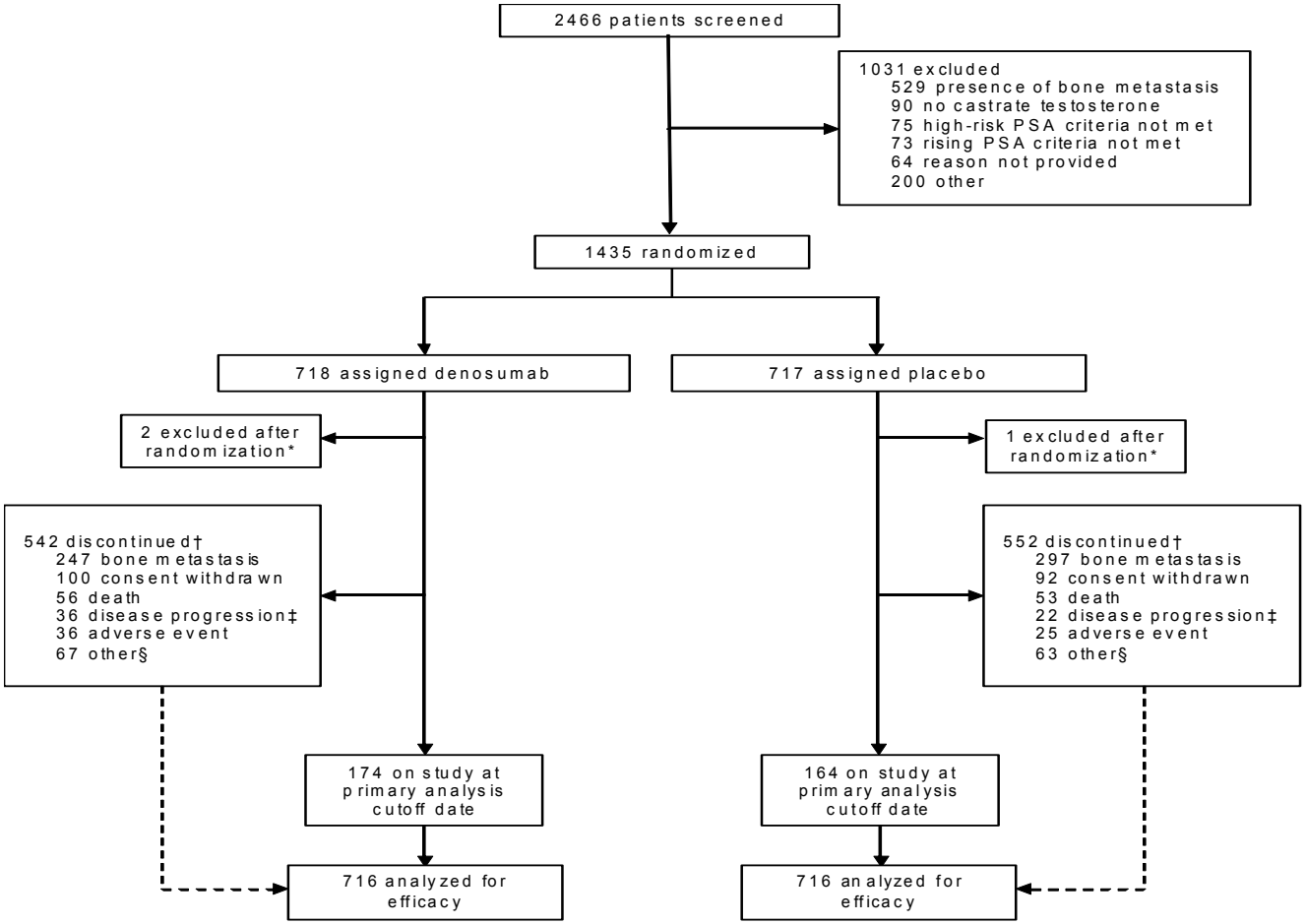
6.3 Study 20050147 Subject Disposition and Baseline Characteristics

A total of 1432 subjects were randomized in the study (716 subjects in each treatment group) and included in the efficacy analyses. Subject disposition is summarized in Figure 4. As of the primary analysis cutoff date, 542 subjects (75.7%) and 552 subjects (77.1%) in the denosumab and placebo groups, respectively, had discontinued from the study regardless of whether they had met the primary endpoint. For the 28.1% of subjects who discontinued without meeting the primary endpoint, the most frequently cited reasons were (denosumab, placebo) study consent withdrawn (12.8%, 12.2%), adverse event (4.9%, 3.5%), and disease progression that precluded continuation of the study (3.9%, 2.5%) (Table 4). Data for evaluation of overall survival was not available for subjects who withdrew full consent or were lost to follow-up (14.5% denosumab, 14.1% placebo) among all randomized subjects.

All study participants were adults and were required to have hormone-refractory (castration-resistant) prostate cancer demonstrated during continuous ADT/post-orchiectomy and to be at high risk for development of bone metastases (PSA value ≥ 8.0 ng/mL no more than 3 months before randomization or PSA doubling time ≤ 10 months). Approximately 80% of subjects had a PSA doubling time ≤ 10 months. Those who did not meet this criterion met the alternative eligibility criterion of a PSA value ≥ 8.0 ng/mL.

Demographics and baseline disease characteristics, including key prognostic factors and cancer therapies received prior to enrollment, were overall generally similar between the denosumab and placebo groups. All subjects in the study were men, and 85% of subjects were white with three quarters coming from North America and Europe. The median (range) age was 74 (44 to 97) years. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 was an eligibility criteria. Key baseline disease characteristics are summarized in Table 5.

Figure 4. Subject Disposition (Study 20050147 Full Analysis Set)



*Review activities and oversight of institutional review board not ensured. †Patients who no longer participated in monthly assessments; patients who withdrew consent or were lost to follow-up were not followed for survival. ‡Not in bone. §Administrative decision, noncompliance, lost to follow-up, protocol deviation, or ineligibility established.

Table 4. Reasons for Study Discontinuation for Subjects Without On-study Bone Metastasis or Death
(Study 20050147, Full Analysis Set)
(Primary Analysis Dataset)

	Placebo (N = 716) n (%)	Denosumab 120 mg Q4W (N = 716) n (%)	All (N = 1432) n (%)
Number of subjects without on-study bone metastasis or death	346 (48.3)	381 (53.2)	727 (50.8)
On study through primary data analysis cutoff date	159 (22.2)	165 (23.0)	324 (22.6)
Discontinued prior to primary data analysis cutoff date	187 (26.1)	216 (30.2)	403 (28.1)
Consent withdrawn	87 (12.2)	92 (12.8)	179 (12.5)
Adverse event	25 (3.5)	35 (4.9)	60 (4.2)
Disease progression[b]	18 (2.5)	28 (3.9)	46 (3.2)
Other	19 (2.7)	27 (3.8)	46 (3.2)
Administrative decision	20 (2.8)	18 (2.5)	38 (2.7)
Noncompliance	8 (1.1)	6 (0.8)	14 (1.0)
Lost to follow-up	8 (1.1)	4 (0.6)	12 (0.8)
Protocol deviation	0 (0.0)	3 (0.4)	3 (0.2)
Ineligibility determined	1 (0.1)	2 (0.3)	3 (0.2)
Protocol-specified criteria[a]	1 (0.1)	1 (0.1)	2 (0.1)

Percentages based on number of subjects randomized
[a] Two subjects were categorized as bone metastasis on EOS CRF page, but not confirmed by central reader.
[b] Disease progression excluding bone metastasis

Program: /stat/amg162/b_mets/20050147/analysis/final/adhoc/program/t_ah_accnt_disp_study_bmdth.sas Output: t14-01_503_ah_accnt_disp_study_bmdth.rtf (Date Generated: 04APR2011:17:27:00) Source Data: adam.aslinfo

Table 5. Summary of Key Baseline Characteristics and Disease History (Study 20050147 Full Analysis Set)

	Placebo (N = 716)	Denosumab 120 mg Q4W (N = 716)	All (N = 1432)
PSA doubling time ≤ 10 months – n (%)	580 (81.0)	574 (80.2)	1154 (80.6)
Median (Q1, Q3) PSA doubling time (months)	5.1 (2.8, 8.6)	5.2 (2.9, 8.5)	5.1 (2.9, 8.6)
Median (Q1, Q3) PSA (ng/mL)	12.5 (4.9, 28.5)	12.2 (4.7, 27.5)	12.3 (4.8, 28.2)
PSA value ≥ 8.0 ng/mL within 3 mo nths prior to randomization - n (%)	471 (65.8)	473 (66.1)	944 (65.9)
PSA level ≥ 8 ng/mL and PSA doubling time ≤ 10 months - n (%)[a]	346 (48.3)	346 (48.3)	692 (48.3)
Received prior chemotherapy regimen - n (%)	54 (7.5)	63 (8.8)	117 (8.2)
Median (Q1, Q3) time from initial diagnosis to randomization (years)	6.1 (3.6, 9.5)	6.1 (3.5, 9.1)	6.1 (3.6, 9.3)
Median (Q1, Q3) ADT duration at study entry (months)	47.1 (27.5, 77.5)	47.2 (27.0, 74.9)	47.1 (27.3, 76.2)
Regional lymph node at initial diagnosis - n (%)			
N0	331 (46.2)	331 (46.2)	662 (46.2)
N1	68 (9.5)	87 (12.2)	155 (10.8)
Nx	317 (44.3)	298 (41.6)	615 (42.9)
Gleason score at diagnosis - n (%)			
2-7	432 (60.3)	404 (56.4)	836 (58.4)
8-10	214 (29.9)	237 (33.1)	451 (31.5)
Missing	70 (9.8)	75 (10.5)	145 (10.1)
No pain or mild pain at worst - n (%)	534 (74.6)	549 (76.7)	1083 (75.6)

N = Number of subjects randomized
Percentages based on number of subjects randomized

ADT = androgen deprivation therapy; PSA = prostate-specific antigen, Q1 and Q3 = interquartile range
[a] Per randomization.
Source: Table 14-1.501, Table 14-2.25, Table 14-2.25.1, Table 14-2.30.3, Table 14-2.31

6.4 Study 20050147 Efficacy Results

6.4.1 Primary Endpoint

Denosumab significantly prolonged bone metastasis-free survival in men with CRPC at high risk of bone metastases. The median bone metastasis-free survival time was 4.2 months longer for subjects who received denosumab compared with subjects who received placebo (29.5 months vs 25.2 months). The risk reduction was 15% relative to placebo (hazard ratio of 0.85 [95% confidence interval (CI): 0.73, 0.98]; p-value = 0.0284) (Table 6). Kaplan-Meier curves for the 2 treatment groups diverged early and continued to separate, indicating that the treatment effect was sustained over time (Figure 5). A total of 335 subjects (46.8%) receiving denosumab and 370 subjects (51.7%) receiving placebo developed a bone metastasis or died during the primary blinded treatment period.

Table 6. Summary of Primary and Secondary Efficacy Endpoint Results (Study 20050147 Full Analysis Set)

	Denosumab vs Placebo (Hazard Ratio)[a]	
Endpoint	Pt Est (95% CI)	p-value
Bone metastasis-free survival time	0.85 (0.73, 0.98)	0.0284
Time to first bone metastasis (either symptomatic or asymptomatic), excluding deaths	0.84 (0.71, 0.98)	0.0317
Overall survival	1.01 (0.85, 1.20)	0.9125

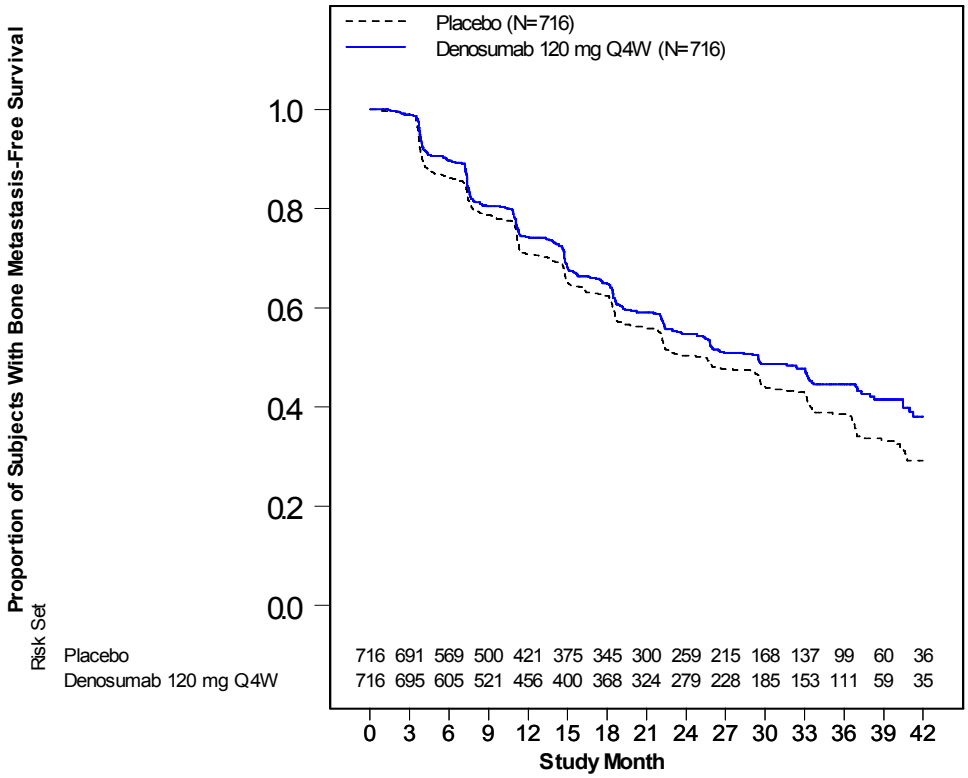
Full Analysis Set used for all endpoints

Pt Est = point estimate, CI = confidence interval

[a] Hazard ratio or rate ratio < 1 favors denosumab.

Source: Table 14-4.1.1, Table 14-4.2.1, and Table 14-4.3.1

**Figure 5. Bone Metastasis-free Survival (Kaplan-Meier Curves)
(Study 20050147 Full Analysis Set)**



N = Number of subjects randomized

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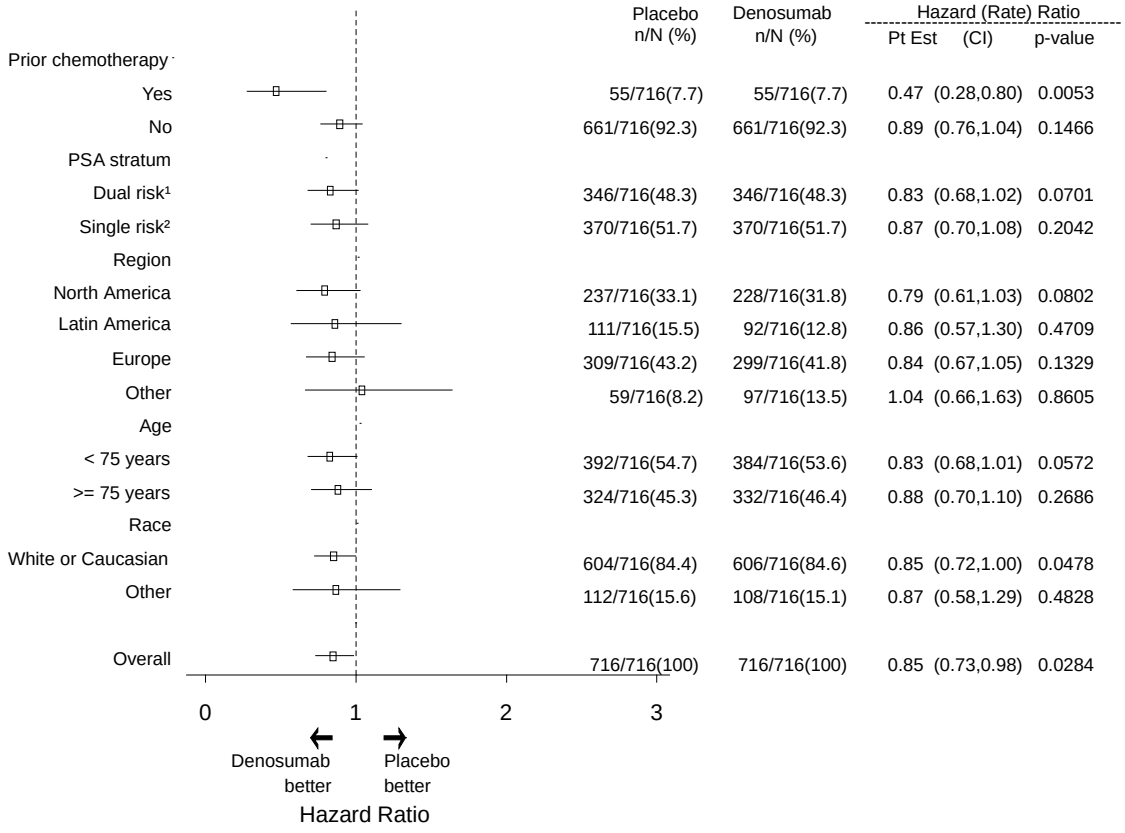
Output: g14-04_001_001_bmf_survival_fas.cgm (Date Generated: 27JAN2011:20:41:13)
Source Data: adam.asleff**

Bone metastasis-free survival time was analyzed within the following prespecified subgroups including baseline characteristics of age, ethnicity, region, and the stratification factors of PSA risk stratum and prior chemotherapy. These subgroup analyses demonstrated that denosumab's effect in prolonging bone metastasis-free survival was consistent across a broad range of evaluations (Figure 6).

Figure 6. Forest Plot of Subgroup Analysis Results of Bone Metastasis-free Survival (Full Analysis Set)



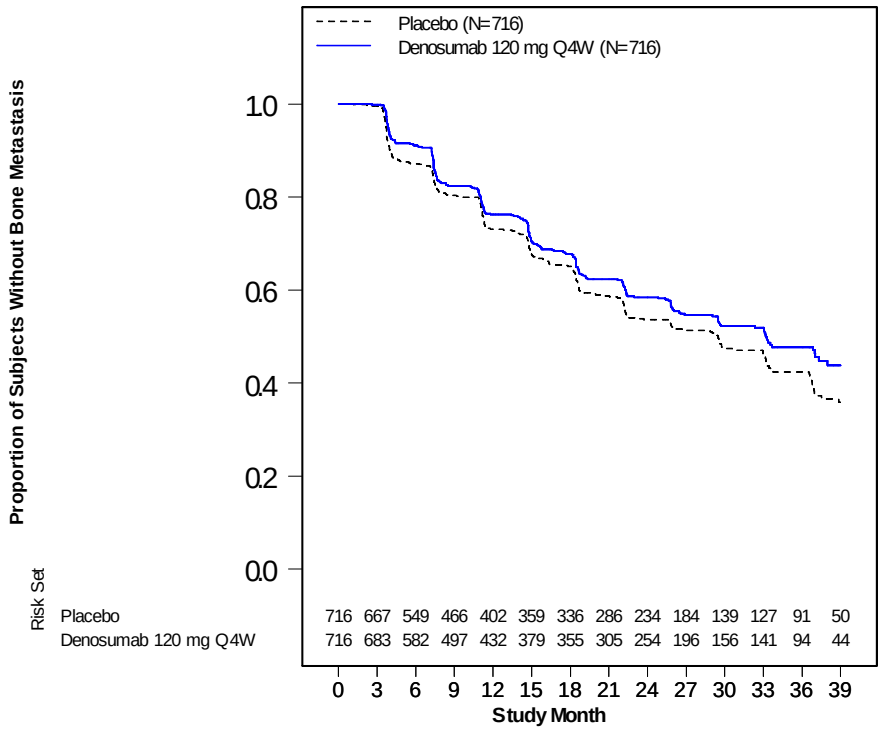
Hazard ratio and 95% CI from a Cox proportional hazards model stratified by the randomization stratification variables
Dual risk[1]: PSA level >= 8 ng/ml and PS A doubling time <= 10 months
Single risk[2]: (PSA level < 8 ng/ml and PS A doubling time <= 10 months) or (PS A level >= 8 ng/ml and PS A doubling time > 10 months)

Program: /stat/amg162/b_mets/20050147/analysis/final/adhoc/program/g_ah_bmt_bygrp.sas
Output: g14-04_003_501_ah_bmt_forest_bygrp_bms.cgm (Date Generated: 17MAR20 11:14:23:39)
Source Data: adam.aslinfo, adam.asleff

6.4.2 Secondary Endpoints

Denosumab also significantly reduced the risk of developing a first bone metastasis by 16% relative to placebo (hazard ratio of 0.84 (95% CI: 0.71, 0.98); p-value = 0.0317) (Table 6 and Figure 7). The median time to bone metastasis was 3.7 months longer for subjects who received denosumab compared with subjects who received placebo (33.2 months versus 29.5 months).

**Figure 7. Time to First Bone Metastasis (Kaplan-Meier Curves)
(Study 20050147 Full Analysis Set)**

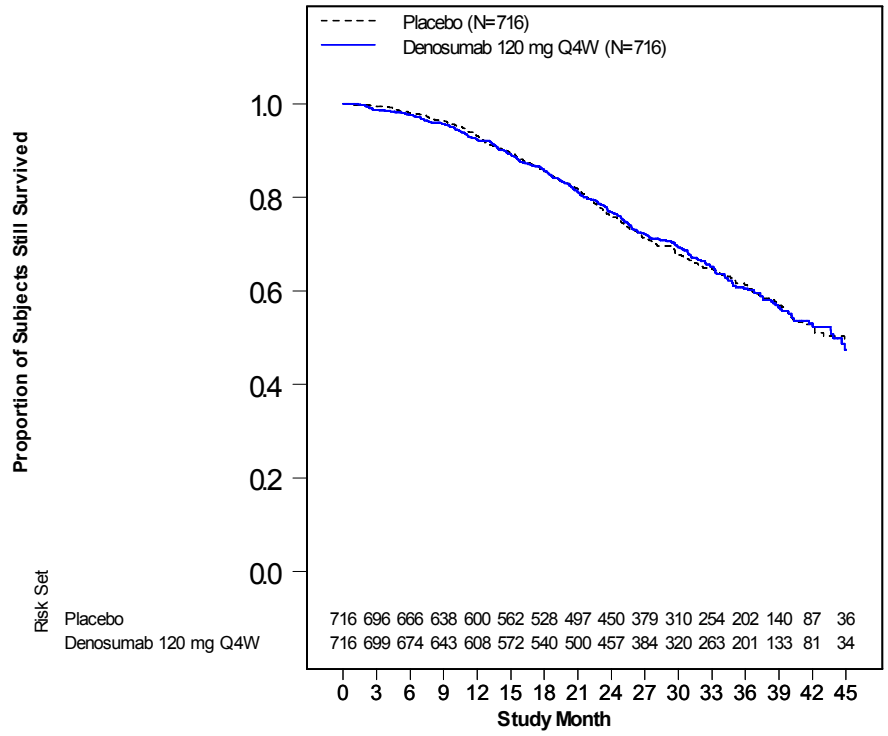


N = Number of subjects randomized

**Program: /stat/amg162/b_mets/20050147/analysis/final/graphs/program/g_bm_time.sas
Output: g14-04_001_003_bm_time_fas.cgm (Date Generated: 27JAN2011:20:41:20)
Source Data: adam.asleff**

Overall survival (including deaths on-study and in follow-up) was balanced between treatment groups (hazard ratio of 1.01 [95% CI: 0.85, 1.20]; p-value = 0.9125) (Table 6 and Figure 8). It is important to note that the study design required discontinuation of investigational product following development of bone metastases so that subjects could receive treatment for prevention of SREs (during the time the trial was conducted, denosumab was not approved for this use). Systemic cancer treatments also could have been initiated. Most deaths (approximately 80%) included in the overall survival endpoint occurred in subjects who had discontinued investigational product, and the Kaplan-Meier estimate of the median time from development of bone metastasis to death was 19 months. In addition, multiple agents could have been used during this period to prolong survival (information on use of these agents was not collected). Thus, the potential to measure any impact of study treatment on subsequent survival was limited.

**Figure 8. Overall Survival (Kaplan-Meier Curves)
(Study 20050147 Full Analysis Set)**



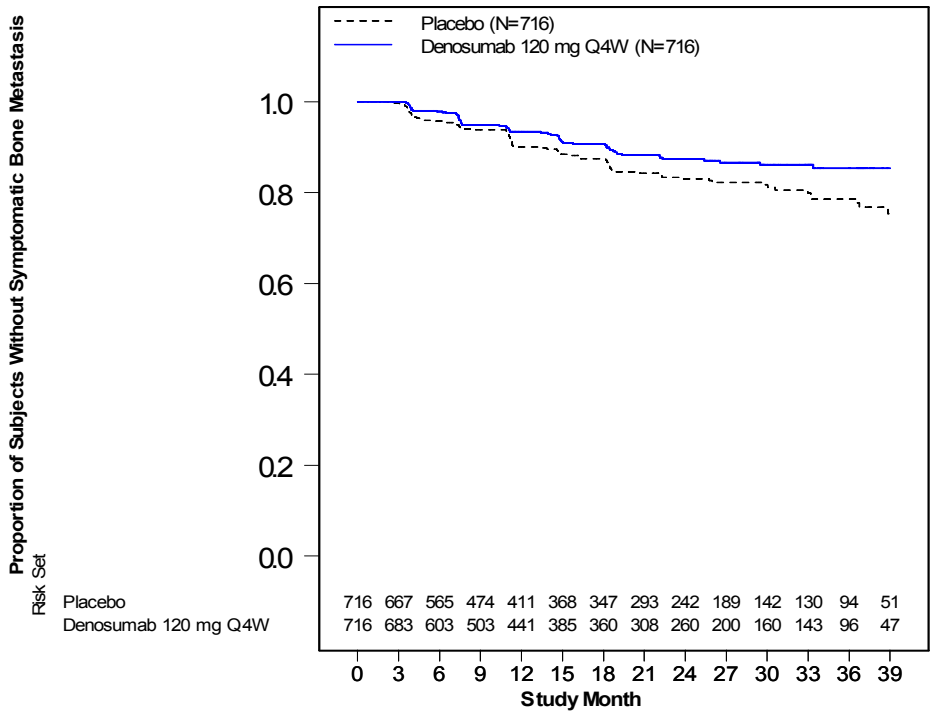
N = Number of subjects randomized

Program: /stat/amg162/b_mets/20050147/analysis/final/graphs/program/g_oa_survival.sas
Output: g14-04_001_005_oa_survival_fas.cgm (Date Generated: 08DEC2010:23:53:50)
Source Data: adam.asleff

6.4.3 Key Exploratory Endpoints

Further supporting the clinical relevance of the effects of denosumab in this high-risk subject population, fewer subjects in the denosumab group (69 [9.6%]) developed symptomatic bone metastases at detection than in the placebo group (96 [13.4%]; p-value = 0.0312). In a post hoc analysis, the time to symptomatic bone metastasis was longer for subjects who received denosumab compared with placebo (hazard ratio of 0.67 [95% CI: 0.49, 0.92]; p-value = 0.0127) (Figure 9). The median time to symptomatic bone metastasis was not reached: at the 25th percentile, the time to symptomatic bone metastasis was 4.4 months longer for subjects who received denosumab compared with subjects who received placebo.

Figure 9. Time to Symptomatic Bone Metastasis (Kaplan-Meier Curves) (Study 20050147 Full Analysis Set)

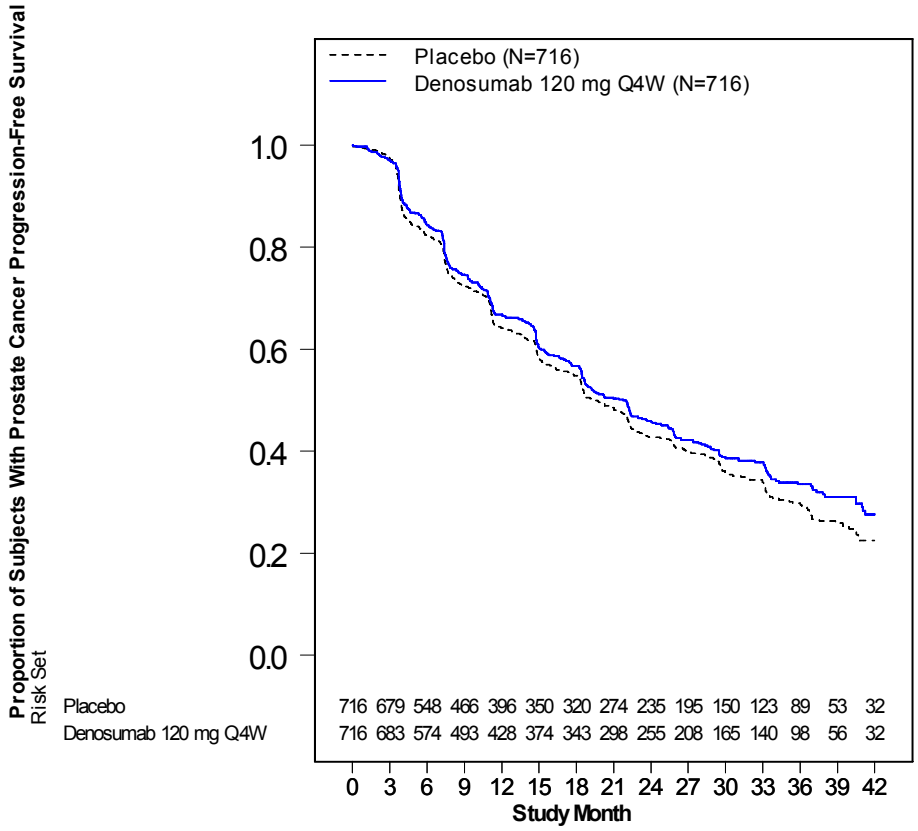


N = Number of subjects randomized

Program: /stat/amg162/b_mets/20050147/analysis/final/adhoc/program/g_ah_sbm_time.sas
Output: g14-04_002_502_ah_sbm_time_lastbonescan.cgm (Date Generated: 14DEC2010:16:24:32)
Source Data: adam.aslinfo, adam.asleff, sdtm.df

Progression-free survival was directionally favorable in the denosumab group, although the differences between groups did not reach statistical significance (Figure 10). Prostate-specific antigen increased over time similarly in both treatment groups (Figure 11).

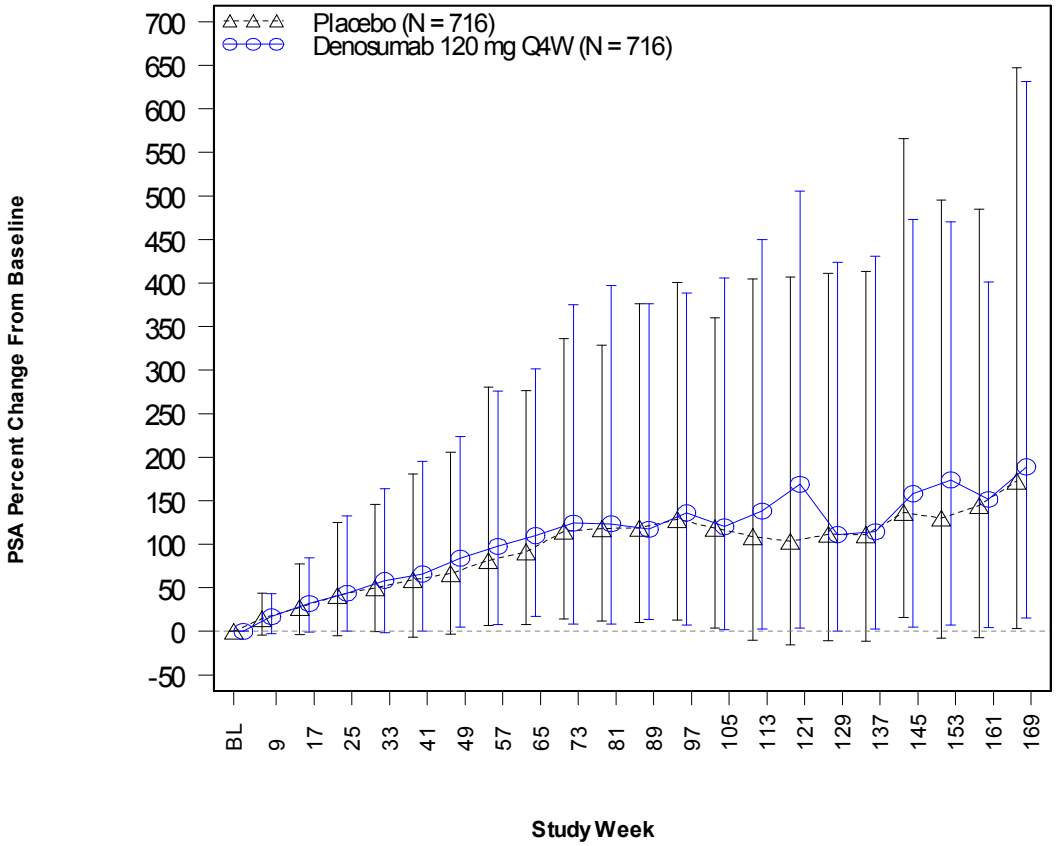
Figure 10. Prostate Cancer Progression-free Survival (Study 20050147 Full Analysis Set)



N = Number of subjects randomized

Program: /stat/amg162/b_mets/20050147/analysis/final/graphs/program/g_bm_time.sas
Output: g14-04_001_008_pd_time_fas.cgm (Date Generated: 27JAN2011:20:41:20)
Source Data: adam.asleff

**Figure 11. PSA Percent Change From Baseline by Visit
Median and Interquartile Ranges
(Study 20050147 Full Analysis Set)**



N = Number of subjects randomized

Program: /stat/amg162/b_mets/20050147/analysis/final/adhoc/program/g_ah_psa_sum.sas
Output: g14-04_001_503_ah_psa_sum_psa_pctchg.cgm (Date Generated: 04FEB2011:14:49:33)
Source Data: adam.aslinfo, adam.albsaf

The subject incidence of vertebral fracture was lower in the denosumab group (7.4%) compared with the placebo group (8.3%); however, the difference was not statistically significant. The assessment of vertebral fractures in this study was limited by the use of multiple types of diagnostic images other than x-rays (eg, CT, MRI) to assess vertebral fractures, the absence of any adjudication, and the protocol-mandated requirement for discontinuation of investigational product when a bone metastasis developed. The hazard ratio for time to nonvertebral fracture (hazard ratio of 0.82 [95% CI: 0.59, 1.14]; p-value = 0.2418) was directionally in favor of denosumab, but the difference did not reach statistical significance.

At study entry, subjects had low pain scores and good performance status. It is important to note the design of Study 20050147 precludes a complete description of the subject experience and thus limits the interpretation of PRO results with regards to the

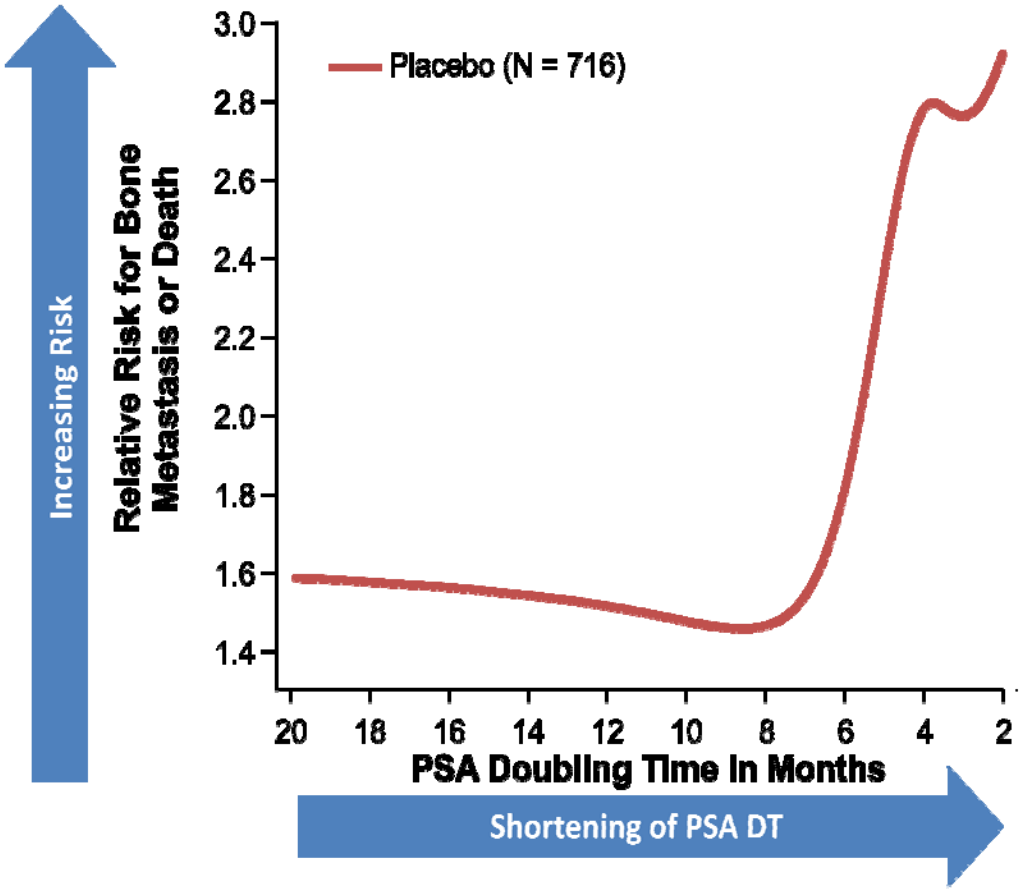
development and subsequent consequences of bone metastases. Of particular importance are: 1) discontinuation of subjects from study/treatment at confirmation of bone metastases with limited PRO data collected after the event of interest; and 2) analyses of PRO data up to the visit when 30% of subjects withdrew due to death, disease progression, or consent withdrawal (week 65), which is significantly shorter than the median time to bone metastases observed in the study. This time point for analysis was decided a priori to minimize the effects of non-random discontinuation and also to minimize the amount of imputation.

The times to worsening pain and to moderate or severe pain were shorter for subjects who developed bone metastases on study compared with subjects without bone metastases (hazard ratios= 0.83 [95% CI: 0.71, 0.96] and 0.76 [95% CI: 0.65, 0.89], respectively; p-value = 0.0119 and 0.0006, respectively, in favor of subjects without bone metastases). Similar results were observed for those subjects who developed symptomatic bone metastases. Changes in pain were generally similar between the denosumab and placebo groups, except for subjects with no or mild pain at baseline, for whom the proportion that subsequently reported moderate or severe worst pain at each visit was consistently lower in the denosumab group than in the placebo group after week 9.

6.4.4 Additional Analyses

All patients enrolled in Study 20050147 were at high risk for development of bone metastases based on published PSA criteria (Smith et al, 2005). Prostate-specific antigen doubling time was further highlighted at the 14 September ODAC meeting as a predictor of risk of bone metastases in this patient population. To evaluate this relationship within the Study 20050147 population, an analysis of the risk of bone metastasis-free survival plotted by PSA doubling time as a continuous variable in the placebo group was performed, as presented in Figure 12. Using the longest PSA doubling time observed in the study to set the baseline risk for the remainder of the population, this figure shows that risk of bone metastasis or death increased as PSA doubling time shortened, with an inflection occurring below a PSA doubling time of 10 months. This result shows that it is possible to identify men with nonmetastatic CRPC who are at risk for developing metastatic disease to the bone in a short time period using readily measured PSA criteria.

Figure 12. Relative Risk for Bone Metastasis-free Survival Over Prostate-specific Antigen Doubling Time in Placebo Group (Study 20050147 Full Analysis Set)



N = Number of subjects randomized
The curve was generated based on a Cox proportional model with a natural cubic spline of 6 degrees of freedom for the inverse of PSA doubling time

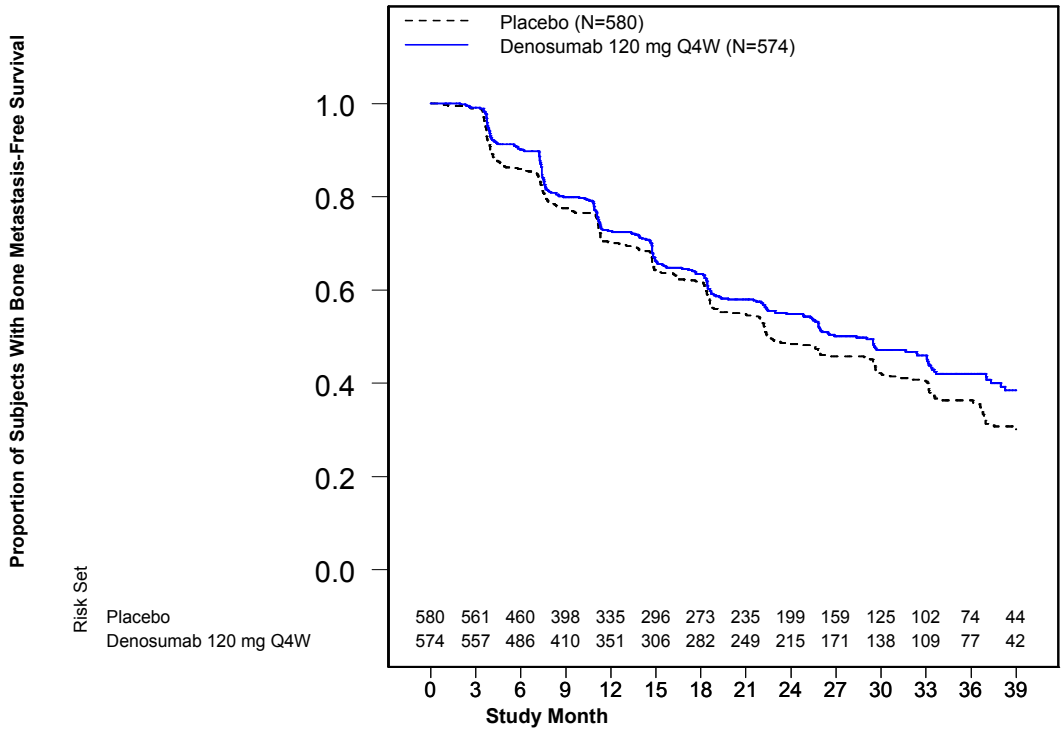
Modified from Figure 04-2.1

Because the risk profile for bone metastasis-free survival in the placebo group showed an inflection occurring below a PSA doubling time of 10 months and a key eligibilty criteria requirement was a PSA doubling time ≤ 10 months, a post hoc analysis of the treatment effect of denosumab compared with placebo was undertaken in this subset of subjects, which represented approximately 80% of the entire study population (N = 1154). (Those who did not meet this criterion met the alternative eligibility criterion of a PSA value ≥ 8.0 ng/mL.) The bone metastasis-free survival time was shorter in this subset than in the overall population, with a median time of 22.4 months for subjects in the placebo group with a PSA doubling time ≤ 10 months compared with 25.2 months for all subjects in the placebo group (2.8 months shorter).

With respect to denosumab's treatment effect, the median bone metastasis-free survival time was 6.0 months longer for those who received denosumab compared with those

who received placebo (28.4 months vs 22.4 months). Denosumab reduced the risk of bone metastasis-free survival by 16% (hazard ratio of 0.84 [95% CI: 0.72, 0.99; p = 0.0423]) (Figure 13). Table 7 shows key efficacy results for this subgroup.

Figure 13. Bone Metastasis-free Survival (Kaplan-Meier Curves) for Subjects With Prostate-specific Antigen Doubling Time ≤ 10 Months (Study 20050147 Subset of Full Analysis Set) (Primary Analysis Data Set)



N = Number of subjects randomized

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Output: g04-01-012-019-bm-surv-si-psa10-l.cgm (Date Generated: 29OCT2011:19:33:35)
Source Data: adam.asleff, adam.aslbas

Table 7. Key Efficacy Results for Subjects With Prostate-specific Antigen Doubling Time ≤ 10 Months (Study 20050147 Subset of Full Analysis Set)

	PSA doubling time ≤ 10 months	
	Denosumab vs Placebo (Hazard Ratio)[a]	
Endpoint	Pt Est (95% CI)	p-value
Bone metastasis-free survival time	0.84 (0.72, 0.99)	0.0423
Time to first bone metastasis (either symptomatic or asymptomatic)	0.85 (0.71, 1.01)	0.0647
Time to symptomatic bone metastasis	0.71 (0.50, 1.00)	0.0501
Overall survival	1.00 (0.83, 1.22)	0.9604
Prostate cancer progression-free survival time[b]	0.88 (0.76, 1.02)	0.0941

All analyses presented are post hoc.
CI = confidence interval; PSA = prostate-specific antigen; Pt Est = point estimate
[a] Hazard ratio or rate ratio < 1 favors denosumab
[b] p-values are adjusted for covariates
Source: Table 4-1.12.13, Table 4-1.12.14, Table 4-1.12.15, Table 4-1.12.16, and Table 4-1.12.17

A second post hoc analysis of the treatment effect of denosumab compared with placebo was also undertaken in the subset of subjects with PSA doubling time ≤ 6 months who are at even higher risk of developing bone metastases or death (Smith et al, 2005).

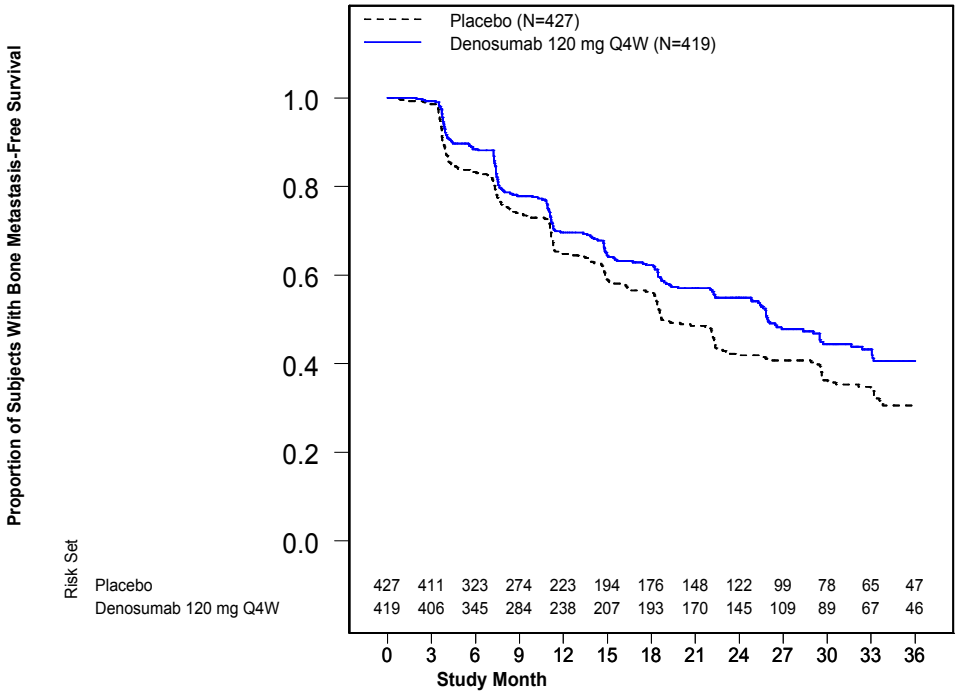
Approximately 60% of the entire study population had a PSA doubling time ≤ 6 months (N = 846). The bone metastasis-free survival time was 7 months shorter in these subjects than in the overall population, with a median time of 18.7 months compared with 25.2 months for all subjects in the placebo group.

The treatment effect was also evaluated in subjects with PSA doubling time ≤ 6 months. The median bone metastasis-free survival time was 7.2 months longer in the denosumab than in the placebo group (25.9 months vs 18.7 months). Denosumab reduced the risk of bone metastasis-free survival by 23% (hazard ratio of 0.77 [95% CI: 0.64, 0.93]; p-value = 0.0064]) (Figure 14 and Table 8).

The bone metastasis-free survival results for the alternate subsets of subjects with PSA doubling time > 10 months and > 6 months are provided in Appendix 2. Tests for interaction did not reach statistical significance (p-values of 0.8008 and 0.0819, respectively).

A third subset of subjects with PSA doubling time ≤ 4 months (Figure 12) was evaluated to complete the analysis of risk versus the treatment effect. This analysis demonstrated similar trends for risk and treatment effects as seen with the other subsets (see Appendix 2).

Figure 14. Bone Metastasis-free Survival (Kaplan-Meier Curves) for Subjects With Prostate-specific Antigen Doubling Time ≤ 6 Months (Study 20050147 Subset of Full Analysis Set)



N = Number of subjects randomized

Program: /stat/amg162/b_mets/20050147/analysis/bla_2011pcprev_reg_prep/graphs/program/g-bm-time-si.sas
Output: g04-01-003-019-bm-surv-si-psa6-l.cgm (Date Generated: 29OCT2011:19:33:35)
Source Data: adam.asleff, adam.aslbas

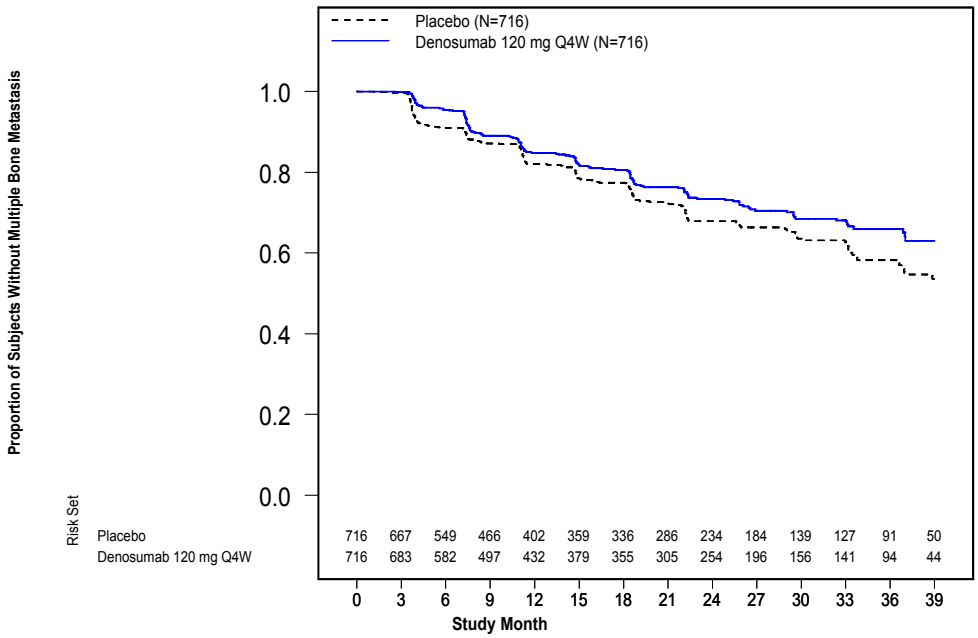
Table 8. Key Efficacy Results for Subjects With Prostate-specific Antigen Doubling Time ≤ 6 Months (Study 20050147 Subset of Full Analysis Set)

	PSA doubling time ≤ 6 months	
	Denosumab vs Placebo (Hazard Ratio)[a]	
Endpoint	Pt Est (95% CI)	p-value
Bone metastasis-free survival time	0.77 (0.64, 0.93)	0.0064
Time to first bone metastasis (either symptomatic or asymptomatic)	0.80 (0.65, 0.97)	0.0257
Time to symptomatic bone metastasis	0.62 (0.42, 0.91)	0.0144
Overall survival	0.99 (0.79, 1.23)	0.8947
Prostate cancer progression-free survival time[b]	0.84 (0.71, 0.99)	0.0378

All analyses presented are post hoc.
CI = confidence interval; Pt Est = point estimate; PSA = prostate-specific antigen
[a] Hazard ratio or rate ratio < 1 favors denosumab.
[b] p-values are adjusted for covariates.
Source: Table 4-1.3.13, Table 4-1.3.14, Table 4-1.3.15, Table 4-1.3.16, and Table 4-1.3.17

Two-thirds of subjects who developed symptomatic bone metastases had > 1 metastasis at detection, and just over half of subjects with asymptomatic metastasis had > 1 metastasis at detection, indicating that those with symptomatic bone metastases were more likely to have multiple bone metastases. A post hoc analysis of the treatment effect of denosumab on time to multiple bone metastases was performed. Denosumab also prolonged time to multiple bone metastases (hazard ratio of 0.76 [95% CI: 0.62, 0.94]; p-value = 0.0107). These results support the findings for time to first bone metastasis and time to symptomatic bone metastasis (Figure 15).

Figure 15. Time to Multiple Bone Metastases (Kaplan-Meier Curves) (Study 20050147 Full Analysis Set)



N = Number of subjects randomized
Subjects who had single site bone metastasis were censored at their bone metastasis date; subjects who did not have any bone met were censored at last image date.

Program: /stat/amg162/b_mets/20050147/analysis/bla_2011pcprev_reg_prep/graphs/program/g-bm-time-ml.sas
Output: g04-01-008-bm-time-mult-l.cgm (Date Generated: 19OCT2011:16:52:11)
Source Data: adam.aslef

Non Bone Metastasis Progression Free Survival and Patterns of Metastases to Non-Osseous Sites

At the request of the FDA, analyses were also performed on time to first non-bone metastasis or death and patterns of metastases. Details of these analyses are provided in Appendix 3. The time to first non-bone metastasis or death was similar between treatment groups (hazard ratio [95% CI] of 1.07 [0.88, 1.30]; p-value = 0.5275). Adjusting for additional covariates of regional lymph node at diagnosis, current lymphatic metastases, T3 –T4 disease, primary local therapy, and prior chemotherapy, the analysis of time to first non-bone metastasis or death resulted in a hazard ratio of 1.03 ([0.85, 1.25], p-value = 0.779). Regarding patterns of metastases, the predominant site of progression outside of the bone is in lymph nodes.

Entire Blinded Treatment Phase Analysis

The results from the exploratory analyses for the entire blinded treatment phase, comprising the primary and extended blinded treatment phases (approximately 5 months

of additional exposure), were directionally consistent with those from the primary analysis, as shown in Table 9.

Table 9. Summary of Key Prostate Cancer Efficacy Endpoints (Study 20050147 Extended Blinded Treatment Analysis)

	Denosumab vs Placebo (Hazard Ratio)[a] (Extended Blinded Treatment Phase Analysis Results)[b]	
Endpoint	Pt Est (95% CI)	p-value
Bone metastasis-free survival time	0.88 (0.76, 1.01)	0.0704
Time to first bone metastasis (either symptomatic or asymptomatic), excluding deaths	0.86 (0.73, 1.00)	0.0517
Time to symptomatic bone metastasis	0.70 (0.52, 0.95),	0.0207
Overall survival	1.06 (0.90, 1.24)	0.5199
Prostate cancer progression-free survival[c]	0.90 (0.79, 1.03)	0.1308

Full Analysis Set used for all endpoints
CI = confidence interval; Pt Est = point estimate
[a] Hazard ratio < 1 favors denosumab
[b] Exploratory analyses from entire blinded treatment analysis through 09 January 2011
[c] p-values are adjusted for covariates
Source: Table 14-4.1.1, Table 14-4.2.1, Table 14-4.2.551, Table 14-4.3.1 and Table 14-4.4.8 of the Study 20050147 Double Blind Extension CSR

7. Clinical Safety of Denosumab

7.1 Exposure to Denosumab

As described in Section 4.3, the primary support for this marketing application is provided by the pivotal, phase 3, placebo-controlled study, Study 20050147. This study provides safety data for 720 subjects who received denosumab (120 mg Q4W) and 705 subjects who received placebo in the primary blinded treatment period, comprising 1271.9 subject-years of exposure to denosumab and 1206.4 subject-years of exposure to placebo. Of the 720 subjects who received denosumab, 504 subjects were exposed to denosumab for a total of ≥ 1 year, 301 subjects were exposed for ≥ 2 years, and 119 subjects were exposed for ≥ 3 years. The median (Q1, Q3) duration on study during the primary blinded treatment period was 20 (10, 31) months for denosumab and 19 (9, 30) months for placebo. The median (Q1, Q3) cumulative exposure was approximately 19 (9 to 30) months for denosumab and 18 (9 to 30) months for placebo.

The 3 pivotal phase 3 SRE studies that supported approval of XGEVA® to prevent SREs in patients with bone metastases from solid tumors, Studies 20050136, 20050244, and 20050103, provide additional safety data. A total of 2841 subjects who received denosumab at the same dose as Study 20050147 (120 mg Q4W) and 2836 subjects who received the active comparator, zoledronic acid (4 mg Q4W), represent 3096.3 subject-years of exposure to denosumab and 3045.6 subject-years of exposure to zoledronic acid. The median (Q1, Q3) cumulative exposure was 12 (5, 19) months for denosumab and 11 (5, 18) months for zoledronic acid. Study 20050103 provides data from subjects with metastatic CRPC. This study included 943 subjects who received denosumab and 945 subjects who received zoledronic acid. These studies provide up to 40.5 months of continuous denosumab exposure.

The pivotal phase 3 study, Study 20040138, in men with nonmetastatic prostate cancer receiving ADT, which supported the approval of Prolia® as treatment to increase bone mass in men at high risk for fracture receiving ADT for nonmetastatic prostate cancer, provides additional safety data for 731 subjects who received denosumab (60 mg Q6M) and 725 subjects who received placebo (Q6M). This study represents 1856.3 subject-years of exposure to denosumab and 1771.9 subject-years of exposure to placebo. The median (Q1, Q3) cumulative exposure was 36 (25, 36) months in the denosumab group and 36 (24, 36) months in the placebo group. This study provides between 1.2 and 39.6 months of continuous denosumab exposure.

7.2 Assessment of Safety

Throughout the denosumab clinical development program, safety was evaluated through the collection of all treatment-emergent adverse events, including serious adverse events, and assessment of their severity, relationship to treatment, time to onset and duration, and outcome.

In addition, hypocalcemia and ONJ, previously identified as risks associated with denosumab treatment at the 120-mg dose in subjects with advanced malignancies and bone metastases, were summarized for Study 20050147. Potential cases of ONJ were reviewed by an independent, external adjudication committee blinded to treatment allocation. A number of other adverse events of interest also were assessed, including infections, new primary malignancy, cardiac/vascular disorders, adverse events potentially associated with hypersensitivity, eczema, and cataracts.

In Study 20050147, hematology and serum chemistry were assessed monthly; central laboratories were used to provide uniform measurements of the key hematology and chemistry parameters used in the analyses of safety. Vital signs measurements (heart rate, systolic and diastolic blood pressure, respiratory rate, and temperature) and ECOG status were assessed quarterly.

Subject safety was monitored on an ongoing basis throughout the study by an external Data Monitoring Committee.

The safety analysis set for Study 20050147 included data from all randomized subjects who received ≥ 1 dose of investigational product. Subjects were analyzed according to their treatment received, regardless of treatment assigned (ie, subjects who received ≥ 1 dose of denosumab were analyzed in the denosumab treatment group).

Relevant safety assessments performed in the pivotal phase 3 SRE studies, Studies 20050136, 20050244, and 20050103, and safety data from Study 20040138 also are presented in this document.

The sections below present key safety information, including adverse events, serious adverse events, deaths, and summaries of specific safety assessments.

7.3 Overall Adverse Events

Denosumab, administered at a dose of 120 mg SC Q4W, had an acceptable safety profile in subjects with CRPC without bone metastases during the primary blinded treatment period of Study 20050147. Consistent with denosumab's mechanism of action, hypocalcemia and ONJ were observed in the denosumab group. These events

were previously identified as risks of denosumab 120 mg Q4W in the advanced cancer clinical program, as reported in the current approved XGEVA® prescribing information (XGEVA®, 2010 in Appendix 1). No new safety risks causally associated with denosumab treatment were identified.

Overall, the subject incidences of adverse events, serious adverse events, fatal adverse events, and grade 3 to 5 adverse events were generally similar between treatment groups (Table 10). As expected given the subjects' underlying cancer and the length of study participation (on average, approximately 20 months for denosumab, 19 months for placebo), most subjects in both treatment groups (94% denosumab, 93% placebo) had at least 1 adverse event. In most cases, adverse events did not lead to withdrawal of investigational product or withdrawal from the study. Subjects with events of ONJ leading to withdrawal from investigational product in the denosumab group accounted for most of the overall difference between treatment groups in withdrawal rates. Also consistent with subjects' disease status, 46% of subjects in each treatment group had a serious adverse event; 53% and 50% of the subjects in the denosumab and placebo groups, respectively, had grade 3 or higher adverse events; and 10% of subjects in each treatment group had fatal adverse events. Adverse events were considered related to investigational product for 26% and 23% of subjects in the denosumab and placebo groups, respectively.

Table 10. Summary of Subject Incidence of Adverse Events (Study 20050147 Safety Analysis Set)

	Placebo (N=705) n (%)	Denosumab 120 mg Q4W (N=720) n (%)
Adverse events regardless of relationship		
All	655 (92.9)	676 (93.9)
Serious	323 (45.8)	329 (45.7)
Fatal	67 (9.5)	73 (10.1)
Leading to study discontinuation	67 (9.5)	79 (11.0)
Leading to investigational product discontinuation	74 (10.5)	90 (12.5)
CTCAE Grade 3, 4, or 5	353 (50.1)	381 (52.9)

CTCAE = Common Terminology Criteria for Adverse Events; N = Number of subjects who received ≥ 1 dose of investigational product; Q4W = once every 4 weeks
CTCAE version 3.0
Includes only treatment-emergent adverse events

Modified from Table T14-6.1.0

7.3.1 Most Common Adverse Events

By preferred term, the most common adverse events in either treatment group were (denosumab, placebo) back pain (23.3%, 22.1%), constipation (17.6%, 16.9%), and arthralgia (17.1%, 15.9%) (Table 11). For comparison, the adverse events reported in the SRE studies are also displayed.

Table 11. Adverse Events by Preferred Term in Descending Order of Frequency (≥ 10% Subject Incidence in Either Treatment Group in Study 20050147)
(Safety Subjects, Integrated Analysis of Safety)

	Study 20050147		Study 20050103		Studies 20050136/20050244/20050103 Combined	
Preferred Term	Placebo (N=705) n (%)	Denosumab 120 mg Q4W (N=720) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Number of subjects reporting adverse events[a]	655 (92.9)	676 (93.9)	918 (97.1)	916 (97.1)	2745 (96.8)	2734 (96.2)
Back pain	156 (22.1)	168 (23.3)	287 (30.4)	304 (32.2)	747 (26.3)	718 (25.3)
Constipation	119 (16.9)	127 (17.6)	251 (26.6)	236 (25.0)	670 (23.6)	603 (21.2)
Arthralgia	112 (15.9)	123 (17.1)	202 (21.4)	194 (20.6)	632 (22.3)	570 (20.1)
Diarrhoea	102 (14.5)	111 (15.4)	152 (16.1)	178 (18.9)	530 (18.7)	577 (20.3)
Urinary tract infection	96 (13.6)	108 (15.0)	124 (13.1)	105 (11.1)	262 (9.2)	220 (7.7)
Oedema peripheral	94 (13.3)	106 (14.7)	174 (18.4)	192 (20.4)	462 (16.3)	472 (16.6)
Urinary retention	79 (11.2)	104 (14.4)	78 (8.3)	88 (9.3)	109 (3.8)	112 (3.9)
Haematuria	100 (14.2)	99 (13.8)	97 (10.3)	88 (9.3)	118 (4.2)	115 (4.0)
Fatigue	79 (11.2)	97 (13.5)	222 (23.5)	257 (27.3)	766 (27.0)	769 (27.1)
Nausea	96 (13.6)	96 (13.3)	245 (25.9)	272 (28.8)	895 (31.6)	876 (30.8)
Asthenia	94 (13.3)	94 (13.1)	239 (25.3)	239 (25.3)	621 (21.9)	607 (21.4)

N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the 20050147 denosumab group and coded using MedDRA Version 13.1.
Q4W = once every 4 weeks
[a] Includes all adverse events, not only those occurring with ≥ 10% frequency

Modified from Table TIAS6-5.1.1

Table 11. Adverse Events by Preferred Term in Descending Order of Frequency (≥ 10% Subject Incidence in Either Treatment Group in Study 20050147)
(Safety Subjects, Integrated Analysis of Safety)

	Study 20050147		Study 20050103		Studies 20050136/20050244/20050103 Combined	
Preferred Term	Placebo (N=705) n (%)	Denosumab 120 mg Q4W (N=720) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Pain in extremity	88 (12.5)	94 (13.1)	196 (20.7)	197 (20.9)	550 (19.4)	524 (18.4)
Anaemia	80 (11.3)	94 (13.1)	341 (36.1)	337 (35.7)	859 (30.3)	771 (27.1)

N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the 20050147 denosumab group and coded using MedDRA Version 13.1.
Q4W = once every 4 weeks
[a] Includes all adverse events, not only those occurring with ≥ 10% frequency

Modified from Table TIAS6-5.1.1

7.3.2 Serious Adverse Events

Serious adverse events were generally similar between treatment groups, were generally reflective of underlying disease, and led to investigational product or study discontinuation in < 6% of subjects in each treatment group. The most common serious adverse events in either treatment group by preferred term in Study 20050147 are presented in Table 12. Serious adverse events from the SRE studies are, again, included for comparison and were generally balanced between treatment groups.

For the serious adverse event of urinary retention, a medical review showed that most cases in each group were associated with an obstructive condition (eg, disease progression and enlarged prostate).

For the serious adverse events of renal failure and renal failure acute, an evaluation of the Medical Dictionary for Regulatory Affairs (MedDRA) high-level term renal failure and impairment which encompasses other renal events that are very similar to acute renal failure (eg, renal failure, acute renal failure, and chronic renal failure), showed that the overall subject incidence was similar in the denosumab group (4.0%) and the placebo group (3.8%). A medical review of cases of renal failure and acute renal failure showed that obstruction was the most common cause of these events in both groups.

For the serious adverse events of hematuria, medical review showed that the majority of cases in each group involved prostate cancer progression or use of other medications that can increase bleeding risk (eg, salicylic acid, clopidogrel, or warfarin).

For the serious adverse events of anemia, medical review showed that the majority of cases in each group involved prostate cancer progression or gastrointestinal bleeding (local infiltration by prostatic cancer, pre-existing ulcerative colitis, or gastric ulcer) or urinary bleeding.

Table 12. Serious Adverse Events by Preferred Term in Descending Order of Frequency (≥ 2% Subject Incidence in Either Treatment Group in Study 20050147)
(Safety Subjects, Integrated Analysis of Safety)

	Study 20050147		Study 20050103		Studies 20050136/20050244/20050103 Combined	
Preferred Term	Placebo (N=705) n (%)	Denosumab 120 mg Q4W (N=720) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Number of subjects reporting serious adverse events[a]	323 (45.8)	329 (45.7)	568 (60.1)	594 (63.0)	1620 (57.1)	1599 (56.3)
Urinary retention	31 (4.4)	54 (7.5)	35 (3.7)	32 (3.4)	44 (1.6)	36 (1.3)
Haematuria	24 (3.4)	35 (4.9)	37 (3.9)	23 (2.4)	39 (1.4)	31 (1.1)
Anaemia	12 (1.7)	22 (3.1)	82 (8.7)	108 (11.5)	163 (5.7)	160 (5.6)
Renal failure	8 (1.1)	16 (2.2)	28 (3.0)	26 (2.8)	50 (1.8)	37 (1.3)
Prostate cancer	21 (3.0)	15 (2.1)	56 (5.9)	34 (3.6)	56 (2.0)	34 (1.2)
Urinary tract infection	14 (2.0)	15 (2.1)	30 (3.2)	28 (3.0)	48 (1.7)	44 (1.5)
Pneumonia	15 (2.1)	12 (1.7)	24 (2.5)	40 (4.2)	93 (3.3)	112 (3.9)
Renal failure acute	15 (2.1)	10 (1.4)	16 (1.7)	18 (1.9)	37 (1.3)	28 (1.0)

N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the 20050147 denosumab group and coded using MedDRA Version 13.1.
Q4W = once every 4 weeks
[a] Includes all adverse events, not only those occurring with ≥ 2% frequency

Program: /stat/amg162/meta/bla_2011pcprev/analysis/css/tables/program/t_ae_pt_cut147.sas
Output: ttias6-13_001_001_sae_ptfreq_2pct_cut20050147.rtf (Date Generated: 11JAN2011:13:11:49) Source Data: adam.aae, adam.aslinfo

7.3.3 Deaths

In Study 20050147, the overall incidence of fatal adverse events was similar between denosumab (10.1%) and placebo (9.5%) and was consistent with the underlying disease state of elderly subjects with CRPC and age-related comorbidities (Table 10). No subject in the denosumab group had a fatal adverse event that was considered to be causally related to denosumab by the investigator.

In addition, overall survival was assessed as a secondary efficacy endpoint in the study, as discussed in Section 6.4.

7.4 Safety Assessments for Adverse Events of Interest

Comprehensive evaluations of adverse events of interest, including hypocalcemia, ONJ, new primary malignancy, cardiovascular events, and adverse events potentially associated with hypersensitivity, eczema, and cataracts were conducted for Study 20050147. Results of these evaluations are discussed in Section 7.4.1 to Section 7.4.3.

7.4.1 Reduction of Serum Calcium and Hypocalcemia

Hypocalcemia is a known risk associated with denosumab treatment due to its mechanism of action to suppress bone resorption and is described in the warnings and precautions section of the current approved XGEVA® prescribing information. Calcium and vitamin D supplementation was strongly recommended in Study 20050147, as in all other phase 3 denosumab studies, to lower the risk of hypocalcemia. Approximately 90% of subjects in the denosumab group and 88% of subjects in the placebo group received calcium and/or vitamin D supplementation.

In the denosumab group, median decreases from baseline in serum calcium generally were ≤ 2% at each visit, and calcium values were ≥ 8 mg/dL for the duration of the treatment phase in 95% of subjects. Common Terminology Criteria for Adverse Effects (CTCAE) grade 3 and 4 low serum calcium values were observed for 1.3% of subjects in the denosumab group and no subjects in the placebo group, and hypocalcemia adverse events were reported for 1.7% of subjects in the denosumab group and 0.3% of subjects in the placebo group (Table 13). One subject in the denosumab group had symptoms (leg cramps) concomitant with the adverse event of hypocalcemia. Across treatment groups, most subjects had events that were mild to moderate in severity, and none of the events were fatal. Only 1 subject (0.1%), who was in the placebo group, had a serious adverse event of hypocalcemia; this was the only subject who discontinued investigational product due to hypocalcemia.

No hypocalcemia adverse events were reported for the 18 subjects (8 denosumab, 10 placebo) who had a baseline creatinine clearance < 30 mL/min. One of these subjects who received denosumab did have a CTCAE grade 4 low serum calcium value.

The incidence of hypocalcemia adverse events in the denosumab group was notably lower than that observed in the denosumab group in Study 20050103 and the SRE integrated analysis set (Table 13). Also, the incidence of grade 3 and 4 low serum calcium values in the denosumab group was lower than in the prostate cancer study, Study 20050103, and the SRE integrated analysis set. These results were not unexpected in this population with less advanced disease, no bone involvement at baseline, and less potential for exposure to nephrotoxic concomitant medications.

Table 13. Summary of Hypocalcemia
(Safety Subjects, Integrated Analysis of Safety)

	Study 20050147		Study 20050103		Studies 20050136/20050244/20050103 Combined	
Adverse Event Category	Placebo (N=705) n (%)	Denosumab 120 mg Q4W (N=720) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Hypocalcemia						
Adverse events	2 (0.3)	12 (1.7)	55 (5.8)	121 (12.8)	141 (5.0)	273 (9.6)

N = Number of subjects who received ≥ 1 dose of investigational product;
Includes only treatment-emergent adverse events
Q4W = once every 4 weeks

Source: *Table TIAS6-25.1*

7.4.2 Osteonecrosis of the Jaw

Osteonecrosis of the jaw is a known risk associated with antiresorptive treatment and is described in the warnings and precautions section of the current approved XGEVA® prescribing information.

Adverse events considered potentially ONJ were identified using a wide search strategy and sent for adjudication to an external panel of independent experts (ONJ Adjudication Committee) who were blinded to treatment allocation and used a predefined set of criteria defining ONJ.

The overall subject incidence of ONJ positively adjudicated by the ONJ Adjudication Committee was 4.6% (33 subjects) and 0% in the denosumab and placebo groups, respectively, in Study 20050147 (Table 14). The overall subject incidence of positively adjudicated ONJ was higher in Study 20050147 than in Study 20050103 and the SRE integrated analysis set (Table 14). However, the median cumulative exposure (Q1, Q3) in the denosumab group was higher in Study 20050147 (19.3 [9.3, 30.4] months) than in the SRE integrated analysis set (12.0 [5.3, 18.9] months) (Section 7.1). When adjusted for exposure, the rates of ONJ were similar across Study 20050147 and the SRE integrated analysis set: across the studies, the cumulative rate of ONJ at year 1 was approximately 1 event per 100 subject-years, and at years 2 and 3, was approximately 2 events per 100 subject-years (Table 15).

Table 14. Summary of Osteonecrosis of the Jaw (Safety Subjects, Integrated Analysis of Safety)

	Study 20050147		Study 20050103		Studies 20050136/20050244/20050103 Combined	
Adverse Event Category	Placebo (N=705) n (%)	Denosumab 120 mg Q4W (N=720) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Osteonecrosis of the Jaw						
Adjudicated positive events	0 (0.0)	33 (4.6)	12 (1.3)	22 (2.3)	37 (1.3)	52 (1.8)

N = Number of subjects who received ≥ 1 dose of investigational product;
Includes only treatment-emergent adverse events
Q4W = once every 4 weeks

Source: *Table TIAS6-26.1*

Table 15. Subject-year Adjusted Positively Adjudicated Osteonecrosis of the Jaw Adverse Events by Time Period for Denosumab-treated Subjects in Study 20050147 and Pooled SRE Studies (Safety Analysis Set)

	0-12 months		0-24 months		0-36 months		Total	
	SRE Studies Pooled (N = 2841) (Subj-yr = 2145.6) n (r)	Study 20050147 (N = 720) (Subj-yr= 636.5) n (r)	SRE Studies Pooled (N = 2841) (Subj-yr = 3175.6) n (r)	Study 20050147 (N = 720) (Subj-yr = 1028.8) n (r)	SRE Studies Pooled (N = 2841) (Subj-yr = 3371.0) n (r)	Study 20050147 (N = 720) (Subj-yr = 1227.7) n (r)	SRE Studies Pooled (N = 2841) (Subj-yr = 3374.4) n (r)	Study 20050147 (N = 720) (Subj-yr = 1273.0) n (r)
Total number of adjudicated positive osteonecrosis of the jaw adverse events reported	22 (1.0)	8 (1.3)	58 (1.8)	21 (2.0)	63 (1.9)	30 (2.4)	63 (1.9)	33 (2.6)

Subj-yr = Total subject-years of follow-up, including the time from the first dose date through the double-blinded cutoff date or first event start date
N = Number of subjects who received ≥ 1 dose of investigational product, n = Number of events, r = Incidence rate per 100 subject-years (n / Subj-yr * 100)
Includes only treatment-emergent adverse events

Program: /stat/amg162/meta/bla_2011pcprev/analysis/css/adhoc/program/t_ah_ae_exp_onj_year_cum.sas
Output: ttias6-01_504_ah_ae_exp_onj_year_cum.rtf (Date Generated: 09FEB2011:13:08:40) Source Data: d09css.aae, d09css.aslinfo, a050147.aae, a050147.aslinfo

Most of the oral events positively adjudicated as ONJ in Study 20050147 were mild or moderate in severity by CTCAE grade: Of the 33 subjects in the denosumab group with positively adjudicated ONJ, 7 subjects (21%) presented with grade 1 events, 16 subjects (48%) presented with grade 2 events, 10 subjects (30%) presented with grade 3 events, and no subjects presented with CTCAE grade 4 or 5 events. Adverse events positively adjudicated as ONJ were reported as serious for 14 (42%) of the 33 subjects.

For the 33 subjects with positively adjudicated ONJ, the median (Q1, Q3) number of denosumab doses received throughout the study was 25 (20, 32) (a median of 22 doses was received before the ONJ event). The median (Q1, Q3) time to onset of the ONJ event was 21 (13, 26) months, and the minimum time to exposed bone was 8.9 months after the first dose of denosumab (data on file at Amgen). Thirty subjects (91%) with ONJ had discontinued denosumab as of the data cut-off date based on the receipt of the end-of-investigational-product case report form.

Subjects who developed ONJ generally had known risk factors for ONJ (Table 16); tooth extraction (70%) was the most frequently reported risk factor. Most of the subjects who developed ONJ had a concurrent local gum or oral infection (23 subjects [70%], data on file), received corticosteroids on study or had a history of corticosteroid use (17 subjects [52%]), and 10 of the subjects (30%) were current smokers at study entry.

Approximately one-third of subjects with ONJ events required no surgical treatments and were managed conservatively (eg, with mouth rinses and antibiotics) (Table 16). For those subjects who required surgical treatments, 64% had surgical procedures that were limited in nature (ie, sequestrectomy, debridement, and curettage); 2 subjects had bone resection. Among all subjects with positively adjudicated ONJ events, the events had resolved (as evidenced by complete mucosal coverage) for 13 subjects (39%) by 01 February 2011 (Table 16); ONJ was ongoing at the time of death for 7 subjects.

For subjects with positively adjudicated ONJ, no notable impact of the ONJ event on pain as measured on the BPI-SF scale (Figure 16) or HRQOL as measured by FACT-G (Figure 17) at scheduled assessments was observed in post hoc analyses.

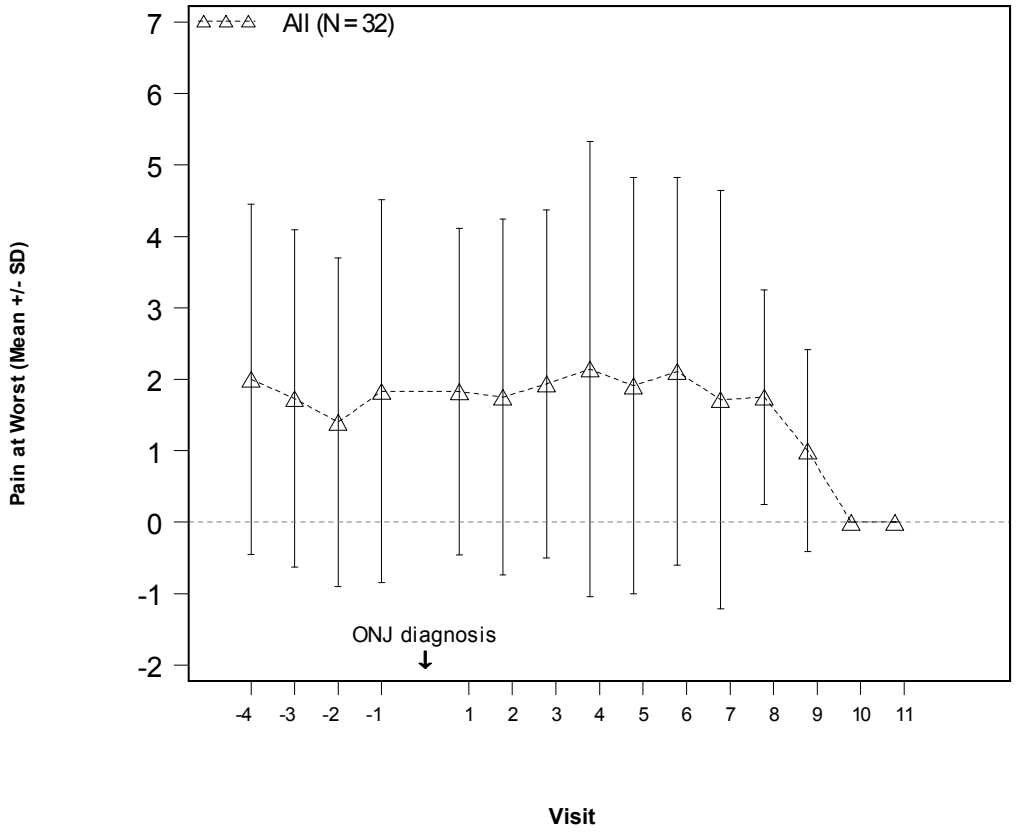
Table 16. Characteristics, Treatment, and Outcomes of Subjects With Positively Adjudicated Osteonecrosis of the Jaw Events in Study 20050147

	Denosumab 120 mg Q4W (N = 33) n (%)
Associated oral events	
Tooth extraction	23 (69.7)
Tooth extraction on study before the ONJ event	21 (63.6)
Poor oral hygiene	18 (54.5)
Use of a dental appliance	16 (48.5)
Any associated oral event	31 (93.9)
Systemic risk factors	
On-study use or history of corticosteroid use [a]	17 (51.5)
Corticosteroid use before the ONJ event	14 (42.4)
Antiangiogenic medication use before the ONJ event	1 (3.0)
Surgical treatment [b]	
None	10 (30.3)
Limited surgical procedures	21 (63.6)
Bone resection	2 (6.1)
Resolution of ONJ [b]	13 (39.4)

N = Number of subjects who received ≥ 1 dose of investigational product and who had positively adjudicated ONJ
n = Number of subjects reporting the events
ONJ = osteonecrosis of the jaw; Q4W = once every 4 weeks
[a] Excluding ocular preparations
[b] As of 01 February 2011

Modified from Table 14-6.8.5, Table 14-6.8.520, Listing 1-6.501

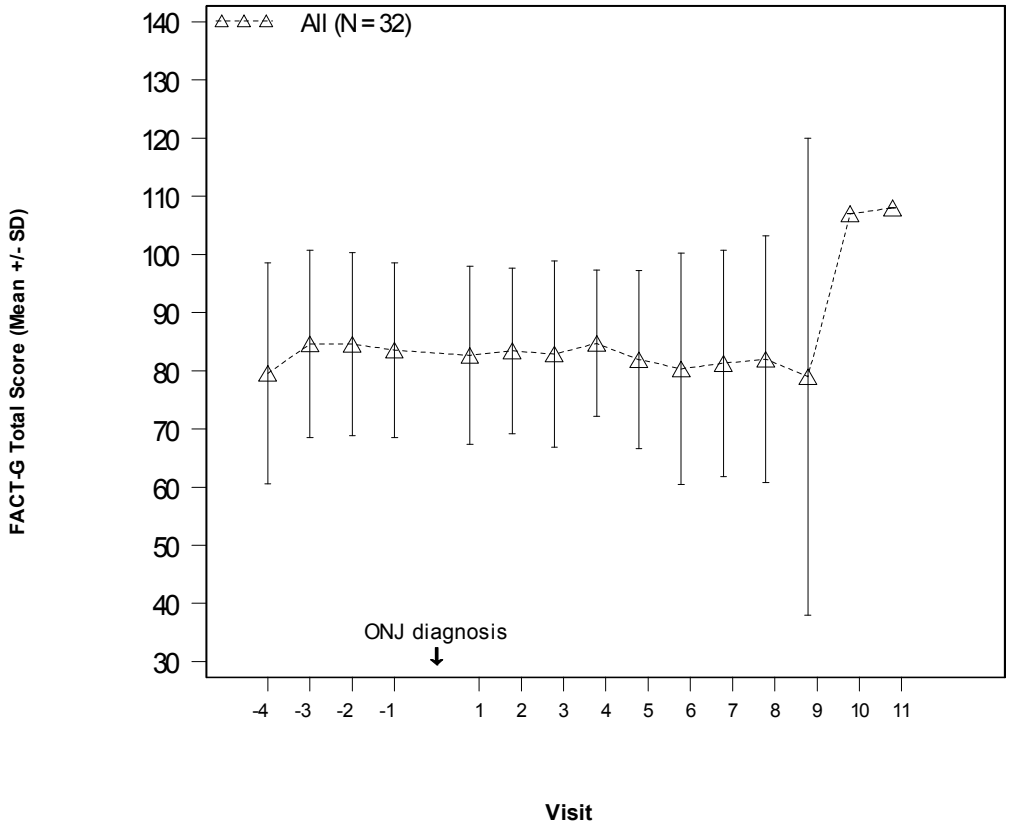
Figure 16. Pain at Worst 6 Months Prior to ONJ Diagnosis and to End-of-study After ONJ Diagnosis (Safety Analysis Set) (20050147 for Primary Analysis)



N = Number of subjects who received >=1 active dose of investigational product, had adjudicated positive osteonecrosis of the jaw, and had >=1 nonmissing data 6 months prior to ONJ and to end-of-study

Program: /stat/amg162/b_mets/20050147/analysis/final/adhoc/program/g_ah_emea_onj_qol.sas
Output: g14-04_009_501_ah_emea_onj_qol_pain_wst.cgm (Date Generated: 16MAY2011:16:17:35)
Source Data: adam.aslinfo, adam.aqsbpi, adam.aqsfact, adam.aae

Figure 17. FACT-G Total Score 6 Months Prior to ONJ Diagnosis and to End-of-study After ONJ Diagnosis (Safety Analysis Set) (20050147 for Primary Analysis)



N = Number of subjects who received >=1 active dose of investigational product, had adjudicated positive osteonecrosis of the jaw, and had >=1 nonmissing data 6 months prior to ONJ and to end-of-study

Program: /stat/amg162/b_mets/20050147/analysis/final/adhoc/program/g_ah_emea_onj_qol.sas
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Source Data: adam.aslinfo, adam.aqsbpi, adam.aqsfact, adam.aae

7.4.3 Other Adverse Events of Interest

No evidence of an increased risk for other adverse events of interest, such as infections, new primary malignancies, cardiac/vascular disorders, adverse events potentially associated with hypersensitivity, eczema, or cataracts was observed for denosumab compared with placebo (Table 17).

Table 17. Summary of Other Adverse Events Of Interest (Safety Subjects, Integrated Analysis of Safety)

	Study 20050147		Study 20050103		Studies 20050136/20050244/20050103 Combined	
Adverse Event Category	Placebo (N = 705) n (%)	Denosumab 120 mg Q4W (N = 720) n (%)	Zoledronic Acid 4 mg Q4W (N = 945) n (%)	Denosumab 120 mg Q4W (N = 943) n (%)	Zoledronic Acid 4 mg Q4W (N = 2836) n (%)	Denosumab 120 mg Q4W (N = 2841) n (%)
All infections						
Adverse events	316 (44.8)	360 (50.0)	375 (39.7)	402 (42.6)	1218 (42.9)	1233 (43.4)
Serious adverse events	58 (8.2)	65 (9.0)	108 (11.4)	130 (13.8)	309 (10.9)	329 (11.6)
Skin Infections						
Adverse events	11 (1.6)	20 (2.8)	27 (2.9)	31 (3.3)	77 (2.7)	84 (3.0)
Serious adverse events	4 (0.6)	5 (0.7)	9 (1.0)	9 (1.0)	19 (0.7)	25 (0.9)
New primary malignancy						
Adverse events	32 (4.5)	38 (5.3)	10 (1.1)	18 (1.9)	18 (0.6)	28 (1.0)
Cardiac disorders						
Adverse events	82 (11.6)	105 (14.6)	160 (16.9)	151 (16.0)	380 (13.4)	381 (13.4)
Serious adverse events	49 (7.0)	56 (7.8)	97 (10.3)	90 (9.5)	192 (6.8)	201 (7.1)
Vascular disorders						
Adverse events	139 (19.7)	178 (24.7)	183 (19.4)	178 (18.9)	598 (21.1)	579 (20.4)
Serious adverse events	27 (3.8)	29 (4.0)	33 (3.5)	34 (3.6)	112 (3.9)	94 (3.3)
Hypersensitivity						
Adverse events	22 (3.1)	25 (3.5)	38 (4.0)	43 (4.6)	108 (3.8)	152 (5.4)

Page 1 of 2

N = Number of subjects who received ≥ 1 dose of investigational product; Q4W = once every 4 weeks
Includes only treatment-emergent adverse events

Source: Table TIAS6-2.1, Table TIAS6-10.1, Table TIAS6-27.1, Table TIAS6-28.1, Table TIAS6-28.2, Table TIAS6-29.1, Table 14-6.10.1 of Study 20050147 CSR, Table 14-6.13.6 of Study 20050103 CSR, Section 2.1.4.4 of Module 2.7.4-AC

Table 17. Summary of Other Adverse Events Of Interest (Safety Subjects, Integrated Analysis of Safety)

	Study 20050147		Study 20050103		Studies 20050136/20050244/20050103 Combined	
Adverse Event Category	Placebo (N = 705) n (%)	Denosumab 120 mg Q4W (N = 720) n (%)	Zoledronic Acid 4 mg Q4W (N = 945) n (%)	Denosumab 120 mg Q4W (N = 943) n (%)	Zoledronic Acid 4 mg Q4W (N = 2836) n (%)	Denosumab 120 mg Q4W (N = 2841) n (%)
Eczema						
Adverse events	20 (2.8)	18 (2.5)	10 (1.1)	9 (1.0)	46 (1.6)	55 (1.9)
Cataract						
Adverse events	21 (3.0)	14 (1.9)	5 (0.5)	4 (0.4)	19 (0.7)	14 (0.5)

N = Number of subjects who received ≥ 1 dose of investigational product; Q4W = once every 4 weeks
Includes only treatment-emergent adverse events

Source: *Table TIAS6-2.1, Table TIAS6-10.1, Table TIAS6-27.1, Table TIAS6-28.1, Table TIAS6-28.2, Table TIAS6-29.1, Table 14-6.10.1 of Study 20050147 CSR, Table 14-6.13.6 of Study 20050103 CSR, Section 2.1.4.4 of Module 2.7.4-AC*

Infections

The subject incidence of adverse events in the MedDRA infection and infestations system organ class was 50.0% in the denosumab group and 44.8% in the placebo group in Study 20050147. The subject incidence of infection was similar between treatment groups in the prostate cancer study, Study 20050103, and in the SRE integrated analysis set. The numerical difference in infection adverse events in Study 20050147 was almost entirely a result of higher subject incidences of osteomyelitis and non-serious upper respiratory tract infections in the denosumab group (differences of 1.7% and 3.2%, respectively). All of the adverse events of osteomyelitis occurred in the jaw, and for 8 of the 12 subjects, all in the denosumab group, these events were adjudicated positive as ONJ. Positively adjudicated adverse events of ONJ are discussed in Section 7.4.2. An evaluation of the MedDRA high-level term upper respiratory tract infections, which encompasses other upper respiratory events that are very similar to upper respiratory tract infections (eg, nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, and pharyngitis), showed that the overall subject incidence was similar in the denosumab group (19.2%) and placebo group (18.3%). Furthermore, the subject incidences of the related preferred terms not included in the high-level term upper respiratory tract infections (ie, influenza-like illness [in the general disorders and administration site conditions systems order class] and upper respiratory tract congestion [in the respiratory, thoracic, and mediastinal disorders systems order class]) were lower in the denosumab group than in the placebo group. Overall, when these similar preferred terms are considered together, an imbalance in upper respiratory tract infection is not observed.

The subject incidence of serious adverse events in the infections and infestations system organ class was 9.0% in the denosumab group and 8.2% in the placebo group (Table 17). Infection adverse events were fatal for 1.0% and 1.3% of subjects in the denosumab and placebo group, respectively.

The subject incidence of adverse events, including serious and fatal events, in the infections and infestations system organ class was similar between treatment groups in Study 20050103 and the SRE integrated analysis set (Table 17).

Overall, no evidence of an increased risk for infection was observed with denosumab compared with placebo.

New Primary Malignancies

In Study 20050147, subject incidence of new primary malignancies was determined in a blinded manner by a manual review of malignancy adverse events in the neoplasm system organ class. The subject incidence of new primary malignancy adverse events in Study 20050147 was similar between treatment groups (5.3% denosumab, 4.5% placebo) (Table 17). No increase in malignancy incidence over time was observed.

Cardiovascular Events

The subject incidence of adverse events in the cardiac disorders system organ class was 14.6% in the denosumab group and 11.6% in the placebo group in Study 20050147 (Table 17).

The subject incidences of individual adverse events, including serious and fatal events, in the cardiac disorders system organ class were similar between treatment groups in Study 20050103 and the SRE integrated analysis set.

Serious myocardial ischemia occurred in 6 subjects (0.8%) in the denosumab group compared with 0 subjects in the placebo group. All 6 subjects with serious myocardial ischemia had 1 or more risk factors for coronary artery disease (ie, hypertension, diabetes, ischemic heart disease, ≥ 70 years of age, former or current smoker, or high cholesterol). There was no increase in the occurrence of serious myocardial ischemia over time. A review of baseline cardiovascular history of the overall population demonstrated that 22.2% of subjects in the denosumab group and 20.7% of subjects in placebo group had a history of coronary artery disease (high-level group term) and 7.5% and 5.0%, respectively, had a history of myocardial ischemia.

Based on the above observations, adjudication of all adverse events in the entire study corresponding to 107 preferred terms potentially indicative of acute coronary syndrome was performed (see Listing 1 of Appendix 4). The adjudication process was conducted by an external, independent, blinded cardiovascular event adjudication committee composed of experienced cardiologists operating under a predefined Cardiovascular Manual of Operations. This adjudication process was well established and extensively used in the denosumab bone loss development program. A total of 165 events were adjudicated (132 subjects). Of these, 30 events occurring in 27 subjects were adjudicated positive as acute coronary syndrome (Listing 2 of Appendix 4). The percentage of events adjudicated positive was low since both non-serious and serious adverse events were sent for adjudication. The subject incidence of positively adjudicated acute coronary syndrome events over the entire blinded treatment phase of

Study 20050147 was similar between treatment groups overall (14 subjects, 1.9% denosumab; 13 subjects, 1.8% placebo). These results are consistent with findings from previous denosumab studies and do not suggest a risk for ischemic cardiac events with denosumab therapy.

The subject incidence of adverse events in the vascular disorders system organ class was 24.7% in the denosumab group and 19.7% in the placebo group in Study 20050147 (Table 17). The most common adverse events in the vascular disorders system organ class in either treatment group were hypertension (7.6% denosumab, 7.1% placebo), hot flush (5.3%, 4.3%), hypotension (2.8%, 2.1%), deep vein thrombosis (2.1%, 0.9%), hematoma (1.9%, 1.1%), flushing (1.0%, 0.7%), lymphoedema (1.0%, 0.3%), and thrombosis (0.4%, 0.9%).

The subject incidence of serious vascular disorder events was similar between the treatment groups (4.0% denosumab, 3.8% placebo) (Table 17). The subject incidences of adverse events, including serious and fatal events, in the vascular disorders system organ class were similar between treatment groups in Study 20050103, the SRE integrated analysis set, and Study 20040138 (Table 17).

Adverse Events Potentially Associated with Hypersensitivity

The subject incidence of adverse events potentially associated with hypersensitivity was similar between treatment groups (3.5% denosumab, 3.1% placebo) in Study 20050147 (Table 17). In general, a review of verbatim terms and timing of the adverse events showed that adverse events potentially associated with hypersensitivity did not appear to be causally or temporally related to initiation of denosumab. Two subjects in each treatment group had events potentially associated with hypersensitivity that were reported as serious, and no fatal adverse events potentially associated with hypersensitivity occurred.

Eczema

The subject incidence of eczema adverse events was similar between treatment groups in Study 20050147 (2.5% denosumab, 2.8% placebo) and in the SRE studies (Table 17).

Cataracts in Men with Prostate Cancer Undergoing Androgen-deprivation Therapy

The subject incidence of the MedDRA preferred term cataract was 1.9% in the denosumab group and 3.0% in the placebo group in Study 20050147 (Table 17). The incidence was similar between treatment groups in Study 20050103. In Study 20040138 in patients with prostate cancer receiving ADT, the overall incidence of cataract adverse

events (reported with the preferred term of cataract) was higher for denosumab (4.7%) compared with placebo (1.2%). Although the incidence of adverse events of cataracts in Study 20040138 may represent a chance finding, Amgen is conducting a phase 3, double-blind, placebo-controlled cataract study in subjects undergoing ADT for nonmetastatic prostate cancer to investigate this adverse event more fully.

7.4.4 Clinical Laboratory and Vital Sign Assessments

As expected with antiresorptive treatment, decreases in albumin-adjusted serum calcium and in serum phosphorus were observed following administration of denosumab in Study 20050147. Serum calcium is discussed further in Section 7.4.1. Median decreases from baseline in serum phosphorus generally were approximately ≤ 10%, and median values remained within the normal range throughout the study. Common Terminology Criteria for Adverse Events grade 3 low phosphorus values were observed for 5.8% of subjects in the denosumab group and 1.8% of subjects in the placebo group; no grade 4 low values were observed. Overall, this incidence of grade 3 and 4 low phosphorus values in the denosumab group was lower than that observed in Study 20050103 and the SRE integrated analysis set.

Changes in other laboratory parameters (eg, hematologic changes) were consistent with the subject's disease background and anticancer therapies, and no changes indicative of a treatment effect for denosumab or placebo were observed in these clinical laboratory parameters. Furthermore, mean and median values of systolic and diastolic blood pressures and heart rate demonstrated no clinically significant effect of denosumab compared with placebo, and changes in ECOG status by visit were similar between treatment groups.

7.4.5 Immunogenicity

Administration of any therapeutic protein has the potential to elicit an immune response. Immunogenicity testing using sensitive and validated assays has been performed in all denosumab clinical studies. The comprehensive clinical immunology evaluations conducted throughout the denosumab clinical program indicate that denosumab poses little risk for immunogenicity. The fully human nature of the denosumab molecule has the potential to reduce the risk of neutralizing antibodies, and therefore, the incidence of antibodies was anticipated to be low.

No neutralizing antibodies against denosumab have been observed to date in the denosumab clinical development program.

7.5 Long-term Safety

Study 20050147 provides data on long-term denosumab exposure. In the primary blinded treatment phase of Study 20050147, 504 subjects were exposed to denosumab for a total of ≥ 1 year, 301 subjects were exposed for ≥ 2 years, and 119 subjects were exposed for ≥ 3 years. The primary blinded treatment phase provides 1.0 to 49.4 months of continuous exposure to denosumab. In addition, the extended blinded treatment phase provides approximately 5 months of additional exposure. Also, the primary blinded treatment phases for Studies 20050136, 20050244, and 20050103 provide between 0.1 and 40.5 months of continuous denosumab exposure, and the extended blinded treatment phases for these studies provide approximately 4 months of additional exposure.

Overall, the results for the double-blind treatment phase in each of these 4 studies were consistent with those from the primary blinded treatment phase. The totality of data from Study 20050147 and the SRE studies indicate that the safety profile of denosumab was consistent over time.

7.6 Clinical Safety of Denosumab in Subsets of Subjects with PSA Doubling Time ≤ 10 Months and ≤ 6 Months

7.6.1 Exposure

In the subset of subjects with PSA doubling times ≤ 10 months, 574 subjects in the denosumab (120 mg Q4W) group and 576 subjects in the placebo group received ≥ 1 dose of investigational product in the primary blinded treatment period. The median (Q1, Q3) duration on study during the primary blinded treatment period was 19 (10, 30) months for denosumab and 18 (9, 29) months for placebo. The median (Q1, Q3) cumulative exposure was approximately 18 (9 to 30) months for denosumab and 18 (8 to 29) months for placebo.

In the subset of subjects with PSA doubling times ≤ 6 months, 419 subjects in the denosumab (120 mg Q4W) group and 425 subjects in the placebo group received ≥ 1 dose of investigational product in the primary blinded treatment period. The median (Q1, Q3) duration on study during the primary blinded treatment period was 18 (9, 29) months for denosumab and 16 (8, 27) months for placebo. The median (Q1, Q3) cumulative exposure was approximately 17 (8 to 28) months for denosumab and 15 (7 to 27) months for placebo.

7.6.2 Assessment of Safety

Overall, the subject incidences of adverse events, serious adverse events, fatal adverse events, and grade 3 to 5 adverse events in the subsets of subjects with PSA doubling times ≤ 10 months and ≤ 6 months were consistent with those in the overall population (Table 18).

Table 18. Summary of Subject Incidence of Adverse Events (For Subjects with PSA Doubling time Less than or Equal to 10 Months and 6 Months in the Safety Analysis Set)

Subjects with PSA doubling times ≤ 10 months	Placebo (N=572) n (%)	Denosumab 120 mg Q4W (N=578) n (%)
Adverse events regardless of relationship		
All	526 (92.0)	541 (93.6)
Serious	258 (45.1)	262 (45.3)
Fatal	54 (9.4)	59 (10.2)
Leading to study discontinuation	59 (10.3)	67 (11.6)
Leading to investigational product discontinuation	64 (11.2)	74 (12.8)
CTCAE Grade 3, 4, or 5	280 (49.0)	307 (53.1)
Subjects with PSA doubling times ≤ 6 months	**Placebo (N=421) n (%)**	**Denosumab 120 mg Q4W (N=423) n (%)**
Adverse events regardless of relationship		
All	380 (90.3)	394 (93.1)
Serious	177 (42.0)	190 (44.9)
Fatal	41 (9.7)	42 (9.9)
Leading to study discontinuation	43 (10.2)	50 (11.8)
Leading to investigational product discontinuation	50 (11.9)	57 (13.5)
CTCAE Grade 3, 4, or 5	190 (45.1)	221 (52.2)

N = Number of subjects who received ≥ 1 dose of investigational product
CTCAE version 3.0
Includes only treatment-emergent adverse events

Modified from Table 06-2.1.1 and Table 06-2.1.2

In the subset of subject with PSA doubling times ≤ 10 months, hypocalcemia adverse events were reported for 1.9% (11 subjects) in the denosumab group and 0.3% (2 subjects) in the placebo group. The subject incidence of ONJ in the denosumab group was 4.5% (26 subjects).

In the subset of subject with PSA doubling times ≤ 6 months, hypocalcemia adverse events were reported for 2.4% (10 subjects) in the denosumab group and 0.5% (2 subjects) in the placebo group. The subject incidence of ONJ in the denosumab group was 4.3% (18 subjects).

7.7 Pharmacovigilance Program

Amgen currently has a systematic and comprehensive pharmacovigilance program in place for XGEVA®, including both routine and proactive pharmacovigilance activities, to monitor the safety profile of denosumab in the oncology setting. Clinical studies in oncology are evaluating the safety of denosumab in approximately 6000 subjects. These include the ongoing open-label extension phase of Study 20050147, which will provide safety data for up to 7 years of continuous exposure to denosumab. In the postmarketing setting, appropriate pharmacovigilance assessments permit additional characterization of the risk profile of denosumab in advanced cancer. No additional postmarketing pharmacovigilance activities are planned beyond those already in place because no new safety risks associated with denosumab were identified in Study 20050147.

Routine pharmacovigilance activities for denosumab currently in place include the following activities:

- assessment of events reported from ongoing clinical studies and postmarketing spontaneously reported events, including use of detailed, targeted questionnaires for specific events (eg, ONJ)
- regular reviews of safety data from clinical studies and spontaneous adverse event reports for safety signal identification
- cumulative reporting of events, including events of interest, to regulatory agencies in periodic safety update reports

Proactive pharmacovigilance activities are performed through ongoing and planned studies that collect additional safety information on hypocalcemia, ONJ, cataracts, hypersensitivity reactions, and immunogenicity. Risk minimization activities are focused on risk communication through labeling, describing the conditions in which denosumab can be used safely and effectively. A summary of pharmacovigilance and risk minimization activities for events of interest are listed in Table 19.

As of 26 November 2011, XGEVA® has been approved for use in the following countries or administrative districts: United States, Canada, European Union, Australia, Russia, and Argentina. In the postmarketing setting, an estimated 15,882 patient-years of

exposure to XGEVA® have occurred through commercial distribution as of the same date cut-off. One case of ONJ has been confirmed in the postmarketing setting. The adverse event information received since approval is consistent with the known safety profile of XGEVA®.

Amgen will continue to monitor the benefit-risk profile of denosumab and the need for additional risk minimization activities, or updates to the prescribing information, on an ongoing basis in all approved indications.

Table 19. Pharmacovigilance and Risk Minimization Activities for Events of Interest

Risk	Pharmacovigilance Activities	Risk Minimization Activities (Prescribing Information)
Hypocalcemia	Routine Surveillance: Assessment of spontaneously reported events (including use of a targeted questionnaire) Cumulative analysis in PSURs Proactive surveillance: Study 20101361 will examine changes in serum calcium levels in subjects with severe renal impairment or receiving dialysis administered multiple 120-mg doses of denosumab	Includes information on the risk of hypocalcemia in the Warnings and Precautions, Special Populations, Adverse Reactions, and Patient Counseling Information sections. Supplementation with calcium and vitamin D was strongly recommended in denosumab advanced cancer studies, and recommendations for such supplementation are included in the prescribing information. Language also is included to correct pre-existing hypocalcemia.
ONJ	Routine Surveillance: Expert medical review of spontaneously reported events and ongoing adjudication in clinical studies Targeted follow-up of spontaneous postmarketing reports using a focused questionnaire Cumulative analysis in PSURs Proactive Surveillance: Ongoing medical reviews and expedited reporting of all reported cases of ONJ EU- and North America-based case registry (Study 20101102) using positively adjudicated events reported from selected sites to monitor the rate and time course of resolution, clinical features, frequency of risk factors, and treatments of ONJ in subjects with advanced cancer in the postmarketing setting	Includes information in the Warnings and Precautions, Adverse Reactions, and Patient Counseling Information sections on the risk of ONJ with denosumab, including management of known risk factors, recommendations for oral examination, avoidance of invasive dental procedures, and oral care by a dentist or oral surgeon if ONJ is suspected.

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ADT = androgen-deprivation therapy; EU = European Union; N/A = not applicable; ONJ = osteonecrosis of the jaw; PSUR = Periodic Safety Update Report

Table 19. Pharmacovigilance and Risk Minimization Activities for Events of Interest

Risk	Pharmacovigilance Activities	Risk Minimization Activities (Prescribing Information)
Infections	Routine Surveillance: Assessment of spontaneously reported events (including use of a targeted questionnaire for infections leading to hospitalization or emergency room visits) Cumulative analysis in PSURs	N/A
Hypersensitivity reactions	Routine Surveillance: Assessment of spontaneously reported events Cumulative analysis in PSURs Proactive surveillance: Evaluation of adverse event profiles (including hypersensitivity adverse events) in subjects who test positive for antidenosumab antibodies in clinical studies and in the postmarketing setting	N/A
Immunogenicity	Proactive Surveillance: Testing for antidenosumab antibodies in all ongoing clinical studies with evaluation of adverse event profiles in subjects who test positive for antidenosumab antibodies During the postmarketing period, testing for antidenosumab antibodies is available for any patient on denosumab at the request of the treating physician	Includes information related to immunogenicity in the Adverse Reactions section

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ADT = androgen-deprivation therapy; EU = European Union; N/A = not applicable; ONJ = osteonecrosis of the jaw; PSUR = Periodic Safety Update Report

Table 19. Pharmacovigilance and Risk Minimization Activities for Events of Interest

Risk	Pharmacovigilance Activities	Risk Minimization Activities (Prescribing Information)
Cataracts in men with prostate cancer receiving ADT	Routine Surveillance: Assessment of spontaneously reported events and prespecified evaluations in men with prostate cancer in ongoing clinical studies 20050103, 20050147, and 20080540 Proactive surveillance: A prospective, randomized, placebo-controlled study is being conducted to further evaluate the incidence of cataracts in men receiving denosumab concurrently with ADT for prostate cancer (Study 20080560)	N/A
Cardiovascular events	Routine Surveillance: Assessment of spontaneously reported events Cumulative analysis in PSURs	N/A
Malignancy	Routine Surveillance: Assessment of spontaneously reported events Cumulative analysis in PSURs	N/A

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ADT = androgen-deprivation therapy; EU = European Union; N/A = not applicable; ONJ = osteonecrosis of the jaw; PSUR = Periodic Safety Update Report

8. Summary and Benefit-Risk Conclusions

Denosumab for the Treatment of Men With Castration-resistant Prostate Cancer at High Risk of Developing Bone Metastases

The development of metastatic disease in men with CRPC is a life-changing event, typically dominated by bone metastases, which are irreversible and progress throughout the remaining period of approximately 2 years of life (Bhandari et al, 2005; de Bono et al, 2010a, 2010b; Kantoff et al, 2010; Tannock et al, 2004). Bone metastases can result in incapacitating complications, which are best represented by SREs (Coleman, 2006). These complications include debilitating pain that often requires aggressive management with radiation therapy and narcotic analgesics, pathologic fractures that may impair ambulation, surgery to prevent or treat pathologic fractures or manage pain, and spinal cord compressions that can result in numbness or weakness, urinary or fecal incontinence, and paralysis. Such progression of disease also confers a significant disease burden to manage the above complications (Fizazi et al, 2011; Saad et al, 2004).

Based on the significant morbidity associated with the development of bone metastases in CRPC and the unique mechanism of action of denosumab in targeting the bone microenvironment, a comprehensive, parallel development program for denosumab in this setting was conducted with the objectives of 1) preventing bone metastases themselves, and 2) preventing the debilitating clinical consequences caused by bone metastases, collectively referred to as SREs. In men with CRPC and established bone metastases (Study 20050103), denosumab 120 mg Q4W demonstrated superior efficacy for reducing the risk of SREs compared with zoledronic acid and supported the approval of denosumab for the prevention of SREs in patients with bone metastases from solid tumors. Patients in Study 20050147 were selected using criteria that conferred a high risk for development of bone metastases, thus reflecting a stage of disease that immediately preceded the population studied in Study 20050103. Results from Study 20050147 demonstrated the efficacy of denosumab in preventing or delaying bone metastases. Specifically, study 20050147 met its primary endpoint with denosumab significantly prolonging median bone metastasis-free survival by 4.2 months with an overall 15% risk reduction, representing a clinically relevant treatment effect of denosumab in this subject population. Further, Study 20050147 demonstrated that it is possible to identify men with nonmetastatic CRPC who are at increasing risk for developing metastatic disease to the bone in a short time period using readily measured PSA criteria. Treatment in the subset of subjects with PSA doubling time ≤ 10 months

(representing approximately 80% of subjects enrolled on the basis of PSA kinetics rather than absolute PSA ≥ 8.0 ng/mL) demonstrated a median bone metastasis-free survival time 6.0 months longer for denosumab compared with placebo with a 16% risk reduction. Treatment in the subset of subjects with PSA doubling time ≤ 6 months demonstrated a median bone metastasis-free survival time 7.2 months longer for denosumab compared with placebo group with a 23% risk reduction. Further supporting the clinical relevance of its effects, denosumab reduced the risk of symptomatic bone metastases by 33% and the risk of multiple bone metastases by 24%.

Although there is debate about the magnitude of the delay in bone metastasis-free survival required to be considered clinically meaningful (14 September 2011 ODAC meeting), the results from this study support the clinical meaningfulness of denosumab's effects in this patient population. Denosumab prolongs bone metastasis-free survival, prevents or delays bone metastases, prevents or delays symptomatic bone metastases, and prevents or delays multiple metastases. Denosumab had a robust treatment effect in patients with increasing risk of bone metastases as PSA doubling times shorten. Denosumab has already demonstrated an ability to prevent or delay SREs in established bone metastases and is approved for use in this setting. Although Study 20050147 was not designed to evaluate SREs after development of bone metastases, the benefit of denosumab is complementary to the already approved benefit of denosumab to prevent SREs in patients with metastatic CRPC.

The intent of Study 20050147 was to confirm that denosumab could prevent bone metastases, a clinically important outcome, based on its bone-targeted mechanism of action; therefore, the focus of design and conduct of the study was on the detection of bone metastases. Death on study prior to the development of bone metastases was included in the primary endpoint in order to account for any potential imbalance in this critical outcome, and overall survival, which included not only deaths on study but also deaths during follow-up, was a secondary endpoint. Overall survival was similar (hazard ratio of 1.01) between the denosumab and placebo groups. Approximately 80% of deaths occurred during the follow-up period (with the Kaplan-Meier estimate of a median time of 19 months from bone metastases to death). The study design required that subjects discontinue investigational product and enter the follow-up phase after the development of bone metastases so that they could receive treatment with approved bone-targeted therapy. Therefore, the potential to measure impact of study treatment on subsequent survival was limited.

The safety profile observed in Study 20050147 was consistent with that described in the current XGEVA® prescribing information. The known safety risks associated with denosumab treatment, hypocalcemia and ONJ, also were observed with denosumab treatment in the 20050147 study. The risks of hypocalcemia and ONJ have been well characterized throughout the development of denosumab, and the XGEVA® prescribing information communicates to healthcare providers appropriate preventive and corrective measures to manage these events. Events of hypocalcemia in the denosumab group were reported for < 2% of subjects. Grade 3 and 4 low serum calcium values (< 7 mg/dL) occurred in 1.3% of subjects treated with denosumab and 0% of subjects treated with placebo. The overall subject incidence of ONJ was higher in this subject population than previously observed with denosumab treatment in subjects with bone metastases in the SRE studies. However, when adjusted for exposure, the rates of ONJ were similar between this study and the SRE studies; the cumulative rate of ONJ at year 1 was approximately 1 event per 100 subject-years, and at years 2 and 3, was approximately 2 events per 100 subject-years. Most ONJ events were mild to moderate in severity, most subjects with ONJ had limited or no surgical procedures, no notable impact of ONJ on pain or HRQOL was observed, and resolution occurred in a meaningful number of subjects (approximately 40%).

Overall Benefit and Risk Conclusions

Despite attempts with the bisphosphonate zoledronic acid (Smith et al, 2005) and the endothelin receptor antagonists atrasentan (Nelson et al, 2008) and zibotentan (AstraZeneca, 2011) to improve clinical outcomes in patients with nonmetastatic CRPC, no therapy has yet been approved for the prevention of metastases including bone metastases in this population.

Denosumab is the first therapy to demonstrate a clinically meaningful benefit in men with nonmetastatic CRPC by preventing or delaying bone metastases. Denosumab has been previously established to delay or prevent the devastating skeletal-related complications of bone metastases. Although no impact on overall survival was observed, the study was not specifically designed to measure the treatment effect of denosumab on this outcome.

The safety profile of denosumab is well characterized. The risks of denosumab in men with nonmetastatic CRPC are consistent with those in patients with advanced cancer and bone metastases treated with denosumab, and include hypocalcemia and ONJ, both of which can be mitigated with proper clinical management.

Collectively, results from Study 20050147 show that denosumab is the first therapy to have a relevant benefit in men with nonmetastatic CRPC by preventing or delaying bone metastases. This benefit is complementary to and consistent with the already approved benefit of denosumab to prevent SREs in patients with metastatic CRPC and, therefore, allows physicians the opportunity to intervene earlier in the prostate cancer treatment continuum to prevent the significant morbidity associated with bone metastases. Furthermore, the results support the use of PSA doubling time to readily identify higher risk patients most likely to benefit from denosumab's ability to delay the development of bone metastases while maintaining a safety profile consistent with that observed in the overall study population, including the risk of ONJ, the most important adverse consequence of inhibition of bone resorption. In conclusion, denosumab offers a novel therapeutic approach to further enhance the chronic management of advanced prostate cancer.

9. References

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XGEVA® (denosumab) [United States Prescribing Information]. Thousand Oaks, CA: Amgen Inc; 2010.

Zometa® (zoledronic acid) [United States Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011.

10. Appendices

Appendix 1. XGEVA® (denosumab) United States Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XGEVA™ safely and effectively. See full prescribing information for XGEVA.

Xgeva (denosumab)
injection, for subcutaneous use
Initial US Approval: 2010

---------- INDICATIONS AND USAGE----------
Xgeva is a RANK ligand (RANKL) inhibitor indicated for:
- Prevention of skeletal-related events in patients with bone metastases from solid tumors (1.1)

Important limitation of use: Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Administer 120 mg every 4 weeks as a subcutaneous injection in the upper arm, upper thigh, or abdomen (2.1)
- Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- 120 mg/1.7 mL (70 mg/mL) single-use vial (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypocalcemia: Severe hypocalcemia can occur in patients receiving Xgeva. Correct hypocalcemia prior to initiating Xgeva. Monitor calcium levels and adequately supplement all patients with calcium and vitamin D (5.1)
- Osteonecrosis of the jaw can occur in patients receiving Xgeva. Perform an oral examination prior to starting Xgeva. Monitor for symptoms. Avoid invasive dental procedures during treatment with Xgeva (5.2)

----------ADVERSE REACTIONS----------
- The most common adverse reactions in patients receiving Xgeva (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy Surveillance Program available (8.1)
- Nursing mothers: May impair mammary gland development and lactation. Discontinue drug or nursing (8.3)
- Pediatric patients: Safety and efficacy not established (8.4)
- Renal impairment: Patients with creatinine clearance less than 30 mL/min or receiving dialysis are at risk for hypocalcemia. Adequately supplement with calcium and vitamin D (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bone Metastasis from Solid Tumors

Xgeva is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

1.2 Important Limitation of Use

Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma *[see Clinical Trials (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of Xgeva is 120 mg administered as a subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen.

Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia *[see Warnings and Precautions (5.1)]*.

2.2 Preparation and Administration

Visually inspect Xgeva for particulate matter and discoloration prior to administration. Xgeva is a clear, colorless to pale yellow solution that may contain trace amounts of translucent to white proteinaceous particles. Do not use if the solution is discolored or cloudy or if the solution contains many particles or foreign particulate matter.

Prior to administration, Xgeva may be removed from the refrigerator and brought to room temperature (up to 25°C/77°F) by standing in the original container. This generally takes 15 to 30 minutes. Do not warm Xgeva in any other way *[see How Supplied/Storage and Handling (16)]*.

Use a 27-gauge needle to withdraw and inject the entire contents of the vial. Do not re-enter the vial. Discard vial after single-use or entry.

3 DOSAGE FORMS AND STRENGTHS

120 mg/1.7 mL (70 mg/mL) single-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypocalcemia

Xgeva can cause severe hypocalcemia. Correct pre-existing hypocalcemia prior to Xgeva treatment. Monitor calcium levels and administer calcium, magnesium, and vitamin D as necessary. Monitor levels more frequently when Xgeva is administered with other drugs that can also lower calcium levels. Advise patients to contact a healthcare professional for symptoms of hypocalcemia *[see Adverse Reactions (6.1) and Patient Counseling Information (17)]*.

Based on clinical trials using a lower dose of denosumab, patients with a creatinine clearance less than 30 mL/min or receiving dialysis are at greater risk of severe hypocalcemia compared to patients with normal renal function. In a trial of 55 patients, without cancer and with varying degrees of renal impairment, who received a single dose of 60 mg denosumab, 8 of 17 patients with a creatinine clearance less than 30 mL/min or receiving dialysis experienced corrected serum calcium levels less than 8.0 mg/dL as compared to 0 of 12 patients with normal renal function. The risk of hypocalcemia at the recommended dosing schedule of 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance less than 30 mL/min or receiving dialysis.

5.2 Osteonecrosis of the Jaw (ONJ)

Osteonecrosis of the jaw (ONJ) can occur in patients receiving Xgeva, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials, 2.2% of patients receiving Xgeva developed ONJ; of these patients, 79% had a history of tooth extraction, poor oral hygiene, or use of a dental appliance *[see Adverse Reactions (6.1)]*.

Perform an oral examination and appropriate preventive dentistry prior to the initiation of Xgeva and periodically during Xgeva therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with Xgeva.

Patients who are suspected of having or who develop ONJ while on Xgeva should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

6 ADVERSE REACTIONS

The following adverse reactions are discussed below and elsewhere in the labeling:

- Hypocalcemia *[see Warnings and Precautions (5.1)]*
- Osteonecrosis of the Jaw *[see Warnings and Precautions (5.2)]*

The most common adverse reactions in patients receiving Xgeva (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (see Table 1).

The most common serious adverse reaction in patients receiving Xgeva was dyspnea.

The most common adverse reactions resulting in discontinuation of Xgeva were osteonecrosis and hypocalcemia.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

The safety of Xgeva was evaluated in three randomized, double-blind, double-dummy trials *[see Clinical Trials (14)]* in which a total of 2841 patients with bone metastasis from prostate cancer, breast cancer, or other solid tumors, or lytic bony lesions from multiple myeloma received at least one dose of Xgeva. In Trials 1, 2, and 3, patients were randomized to receive either 120 mg of Xgeva every 4 weeks as a subcutaneous injection or 4 mg (dose adjusted for reduced renal function) of zoledronic acid every 4 weeks by intravenous (IV) infusion. Entry criteria included serum calcium (corrected) from 8 to 11.5 mg/dL (2 to 2.9 mmol/L) and creatinine clearance 30 mL/min or greater. Patients who had received IV bisphosphonates were excluded, as were patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure. During the study, serum chemistries including calcium and phosphorus were monitored every 4 weeks. Calcium and vitamin D supplementation was recommended but not required.

The median duration of exposure to Xgeva was 12 months (range: 0.1 – 41) and median duration on-study was 13 months (range: 0.1 – 41). Of patients who received Xgeva, 46% were female. Eighty-five percent were White, 5% Hispanic/Latino, 6% Asian, and 3% Black. The median age was 63 years (range: 18 – 93). Seventy-five percent of patients who received Xgeva received concomitant chemotherapy.

Table 1. Per-patient Incidence of Selected[a] Adverse Reactions of Any Severity (Trials 1, 2, and 3)

Body System	Xgeva n = 2841 %	Zoledronic Acid n = 2836 %
GASTROINTESTINAL		
Nausea	31	32
Diarrhea	20	19
GENERAL		
Fatigue/Asthenia	45	46
INVESTIGATIONS		
Hypocalcemia[b]	18	9
Hypophosphatemia[b]	32	20
NEUROLOGICAL		
Headache	13	14
RESPIRATORY		
Dyspnea	21	18
Cough	15	15

[a] Adverse reactions reported in at least 10% of patients receiving Xgeva in Trials 1, 2, and 3, and meeting one of the following criteria:

- At least 1% greater incidence in Xgeva-treated patients, or

- Between-group difference (either direction) of less than 1% and more than 5% greater incidence in patients treated with zoledronic acid compared to placebo (US Prescribing Information for zoledronic acid)

[b] Laboratory-derived and below the central laboratory lower limit of normal [8.3 – 8.5 mg/dL (2.075 – 2.125 mmol/L) for calcium and 2.2 – 2.8 mg/dL (0.71 – 0.9 mmol/L) for phosphorus]

Severe Mineral/Electrolyte Abnormalities

- Severe hypocalcemia (corrected serum calcium less than 7 mg/dL or less than 1.75 mmol/L) occurred in 3.1% of patients treated with Xgeva and 1.3% of patients treated with zoledronic acid. Of patients who experienced severe hypocalcemia, 33% experienced 2 or more episodes of severe hypocalcemia and 16% experienced 3 or more episodes *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

- Severe hypophosphatemia (serum phosphorus less than 2 mg/dL or less than 0.6 mmol/L) occurred in 15.4% of patients treated with Xgeva and 7.4% of patients treated with zoledronic acid.

Osteonecrosis of the Jaw

In the primary treatment phases of Trials 1, 2, and 3, ONJ was confirmed in 1.8% of patients in the Xgeva group and 1.3% of patients in the zoledronic acid group *[see Warnings and Precautions (5.2)]*. When events occurring during an extended treatment phase of approximately 4 months in each trial are included, the incidence of confirmed ONJ was 2.2% in patients who received Xgeva. The median time to ONJ was 14 months (range: 4 – 25).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Using an electrochemiluminescent bridging immunoassay, less than 1% (7/2758) of patients with osseous metastases treated with denosumab doses ranging from 30-180 mg every 4 weeks or every 12 weeks for up to 3 years tested positive for binding antibodies. No patient with positive binding antibodies tested positive for neutralizing antibodies as assessed using a chemiluminescent cell-based *in vitro* biological assay. There was no evidence of altered pharmacokinetic profile, toxicity profile, or clinical response associated with binding antibody development.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of a positive antibody (including neutralizing antibody) test result may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to denosumab with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal drug-drug interaction trials have been conducted with Xgeva.

In clinical trials in patients with breast cancer metastatic to bone, Xgeva was administered in combination with standard anticancer treatment. Serum denosumab concentrations at 1 and 3 months and reductions in the bone turnover marker uNTx/Cr (urinary N-terminal telopeptide corrected for creatinine) at 3 months were similar in patients with and without prior intravenous bisphosphonate therapy.

There was no evidence that various anticancer treatments affected denosumab systemic exposure and pharmacodynamic effect. Serum denosumab concentrations at 1 and 3 months were not altered by concomitant chemotherapy and/or hormone therapy. The median reduction in uNTx/Cr from baseline to month 3 was similar between patients receiving concomitant chemotherapy and/or hormone therapy *[see Clinical Pharmacology (12.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Category C

There are no adequate and well-controlled trials of Xgeva in pregnant women. Use Xgeva during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage women who become pregnant during Xgeva treatment to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

In an embryofetal developmental study, cynomolgus monkeys received subcutaneous denosumab weekly during organogenesis at doses up to 6.5-fold higher than the recommended human dose of 120 mg every 4 weeks, based on body weight (mg/kg). No evidence of maternal toxicity or fetal harm was observed. However, this study only assessed fetal toxicity during the first trimester, and fetal lymph nodes were not examined. Potential adverse developmental effects resulting from exposures during the second and third trimesters have not been assessed in animals *[see Nonclinical Toxicology (13.2)]*.

In genetically engineered mice in which the gene for RANK ligand (RANKL) has been deleted (a "knockout mouse"), the absence of RANKL caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice also showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum *[see Use in Specific Populations (8.3)]*.

8.3 Nursing Mothers

It is not known whether Xgeva is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Xgeva, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Maternal exposure to Xgeva during pregnancy may impair mammary gland development and lactation based on animal studies in pregnant mice lacking the RANK/RANKL signaling pathway that have shown altered maturation of the maternal mammary gland, leading to impaired lactation postpartum *[see Nonclinical Toxicology (13.2)]*.

8.4 Pediatric Use

The safety and effectiveness of Xgeva in pediatric patients have not been established. Treatment with Xgeva may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

In neonatal rats, inhibition of RANKL with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses less than or equal to 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent monkeys dosed with denosumab at 5 and 25 times (10 and 50 mg/kg dose) higher than the recommended human dose of 120 mg subcutaneously every 4 weeks (based on body weight mg/kg) had abnormal growth plates *[see Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use

Of patients who received Xgeva in Trials 1, 2, and 3, 1260 (44%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

In a trial of 55 patients without cancer and with varying degrees of renal function who received a single dose of 60 mg denosumab, patients with a creatinine clearance of less than 30 mL/min or receiving dialysis were at greater risk of severe hypocalcemia with denosumab compared to patients with normal renal function. The risk of hypocalcemia at the recommended dosing schedule of 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance of less than 30 mL/min or receiving dialysis *[see Warnings and Precautions (5.1), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no experience with overdosage of Xgeva.

11 DESCRIPTION

Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human RANKL. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

Xgeva is a sterile, preservative-free, clear, colorless to pale yellow solution.

Each single-use vial of Xgeva contains 120 mg denosumab, 4.6% sorbitol, 18 mM acetate, Water for Injection (USP), and sodium hydroxide to a pH of 5.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Xgeva binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Xgeva prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases.

12.2 Pharmacodynamics

In patients with breast cancer and bone metastases, the median reduction in uNTx/Cr was 82% within 1 week following initiation of Xgeva 120 mg administered subcutaneously. In Trials 1, 2, and 3, the median reduction in uNTx/Cr from baseline to month 3 was approximately 80% in 2075 Xgeva-treated patients.

12.3 Pharmacokinetics

Following subcutaneous administration, bioavailability was 62%. Denosumab displayed nonlinear pharmacokinetics at doses below 60 mg, but approximately dose-proportional increases in exposure at higher doses. With multiple subcutaneous doses of 120 mg every 4 weeks in patients with cancer metastatic to the bone, up to 2.8-fold accumulation in serum denosumab concentrations was observed and steady state was achieved by 6 months. At steady state, the mean ± SD serum trough concentration was 20.5 ± 13.5 mcg/mL at the recommended Xgeva dose, and the mean elimination half-life was 28 days.

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. Denosumab clearance and volume of distribution were proportional to body weight. The steady-state exposure following repeat subcutaneous administration of 120 mg every 4 weeks to 45 kg and 120 kg subjects were, respectively, 48% higher and 46% lower than exposure of the typical 66 kg subject.

Specific Populations
The pharmacokinetics of denosumab were not affected by age, gender, and race. The pharmacokinetics of denosumab in pediatric patients have not been assessed.

Hepatic Impairment: No clinical trials have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of denosumab.

Renal Impairment: In a trial of 55 subjects with varying degrees of renal function, including subjects on dialysis, the degree of renal impairment had no effect on the pharmacokinetics and pharmacodynamics of denosumab *[see Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity
The carcinogenic potential of denosumab has not been evaluated in long-term animal studies.

Mutagenicity
The genotoxic potential of denosumab has not been evaluated.

Impairment of Fertility
Denosumab had no effect on female fertility or male reproductive organs in monkeys at exposures that were 6.5- to 25-fold higher than the observed human dose of 120 mg subcutaneously administered once every 4 weeks (based on body weight mg/kg).

13.2 Animal Toxicology and/or Pharmacology

Denosumab is an inhibitor of osteoclastic bone resorption via inhibition of RANKL. Adolescent nonhuman primates treated with monthly doses of denosumab greater than 5 times the recommended human dose of 120 mg had abnormal growth plates. Because the biological activity of denosumab in animals is specific to nonhuman primates, evaluation of genetically engineered (knockout) mice or use of other biological inhibitors of the RANK/RANKL pathway, OPG-Fc and RANK-Fc, provided additional safety information on the inhibition of the RANK/RANKL pathway in rodent models. A study in 2-week-old rats given the RANKL inhibitor OPG-Fc showed reduced bone growth, altered growth plates, and impaired tooth eruption. These changes were partially reversible in this model when dosing with the RANKL inhibitors was discontinued. Neonatal RANK/RANKL knockout mice also exhibited reduced bone growth and lack of tooth eruption. RANK/RANKL knockout mice also exhibited absence of lymph node formation, as well as an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) *[see Use in Specific Populations (8.3, 8.4)]*.

14 CLINICAL TRIALS

The safety and efficacy of Xgeva for the prevention of skeletal-related events in patients with bone metastases from solid tumors was demonstrated in three international, randomized (1:1), double-blind, active-controlled, noninferiority trials comparing Xgeva with zoledronic acid. In all three trials, patients were randomized to receive 120 mg Xgeva subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose adjusted for reduced renal function). Patients with creatinine clearance less than 30 mL/min were excluded. In each trial, the main outcome measure was demonstration of noninferiority of time to first skeletal-related event (SRE) as compared to zoledronic acid. Supportive outcome measures were superiority of time to first SRE and superiority of time to first and subsequent SRE; testing for these outcome measures occurred if the main outcome measure was statistically significant. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression.

Trial 1 enrolled 2046 patients with advanced breast cancer and bone metastasis. Randomization was stratified by a history of prior SRE (yes or no), receipt of chemotherapy within 6 weeks prior to randomization (yes or no), prior oral bisphosphonate use (yes or no), and region (Japan or other countries). Forty percent of patients had a previous SRE, 40% received chemotherapy within 6 weeks prior to randomization, 5% received prior oral bisphosphonates, and 7% were enrolled from Japan. Median age was 57 years, 80% of patients were White, and 99% of patients were women. The median number of doses administered was 18 for denosumab and 17 for zoledronic acid.

Trial 2 enrolled 1776 adults with solid tumors other than breast and castrate-resistant prostate cancer with bone metastasis and multiple myeloma. Randomization was stratified by previous SRE (yes or no), systemic anticancer therapy at time of randomization (yes or no), and tumor type (non-small cell lung cancer, myeloma, or other). Eighty-seven percent were receiving systemic anticancer therapy at the time of randomization, 52% had a previous SRE, 64% of patients were men, 87% were White, and the median age was 60 years. A total of 40% of patients had non-small cell lung cancer, 10% had multiple myeloma, 9% had renal cell carcinoma, and 6% had small cell lung cancer. Other tumor types each comprised less than 5% of the enrolled population. The median number of doses administered was 7 for both denosumab and zoledronic acid.

Trial 3 enrolled 1901 men with castrate-resistant prostate cancer and bone metastasis. Randomization was stratified by previous SRE, PSA level (less than 10 ng/mL or 10 ng/mL or greater) and receipt of chemotherapy within 6 weeks prior to randomization (yes or no). Twenty-six percent of patients had a previous SRE, 15% of patients had PSA less than 10 ng/mL, and 14% received chemotherapy within

6 weeks prior to randomization. Median age was 71 years and 86% of patients were White. The median number of doses administered was 13 for denosumab and 11 for zoledronic acid.

Xgeva delayed the time to first SRE following randomization as compared to zoledronic acid in patients with breast or castrate-resistant prostate cancer (CRPC) with osseous metastases (Table 2). In patients with bone metastasis due to other solid tumors or lytic lesions due to multiple myeloma, Xgeva was noninferior to zoledronic acid in delaying the time to first SRE following randomization.

Overall survival and progression-free survival were similar between arms in all three trials. Mortality was higher with Xgeva in a subgroup analysis of patients with multiple myeloma (hazard ratio [95% CI] of 2.26 [1.13, 4.50]; n = 180).

Table 2. Efficacy Results for Xgeva Compared to Zoledronic Acid

	Trial 1 Metastatic Breast Cancer		Trial 2 Metastatic Solid Tumors or Multiple Myeloma		Trial 3 Metastatic CRPC[a]	
	Xgeva	Zoledronic Acid	Xgeva	Zoledronic Acid	Xgeva	Zoledronic Acid
N	1026	1020	886	890	950	951
First On-study SRE						
Number of Patients who had SREs (%)	315 (30.7)	372 (36.5)	278 (31.4)	323 (36.3)	341 (35.9)	386 (40.6)
Components of First SRE						
Radiation to Bone	82 (8.0)	119 (11.7)	119 (13.4)	144 (16.2)	177 (18.6)	203 (21.3)
Pathological Fracture	212 (20.7)	238 (23.3)	122 (13.8)	139 (15.6)	137 (14.4)	143 (15.0)
Surgery to Bone	12 (1.2)	8 (0.8)	13 (1.5)	19 (2.1)	1 (0.1)	4 (0.4)
Spinal Cord Compression	9 (0.9)	7 (0.7)	24 (2.7)	21 (2.4)	26 (2.7)	36 (3.8)
Median Time to SRE (months)	NR[b]	26.4	20.5	16.3	20.7	17.1
Hazard Ratio (95% CI)	0.82 (0.71, 0.95)		0.84 (0.71, 0.98)		0.82 (0.71, 0.95)	
Noninferiority p-value	< 0.001		< 0.001		< 0.001	
Superiority p-value[c]	0.010		0.060		0.008	
First and Subsequent SRE[d]						
Mean Number/Patient	0.46	0.60	0.44	0.49	0.52	0.61
Rate Ratio (95% CI)	0.77 (0.66, 0.89)		0.90 (0.77, 1.04)		0.82 (0.71, 0.94)	
Superiority p-value [e]	0.001		0.145		0.009	

[a]CRPC = castrate-resistant prostate cancer.
[b]NR = not reached.
[c]Superiority testing performed only after denosumab demonstrated to be noninferior to zoledronic acid within trial.
[d]All skeletal events postrandomization; new events defined by occurrence ≥ 21 days after preceding event.
[e]Adjusted p-values are presented.

16 HOW SUPPLIED/STORAGE AND HANDLING

Xgeva is supplied in a single-use vial.

120 mg/1.7 mL	1 vial per carton	NDC 55513-730-01

Store Xgeva in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, Xgeva must not be exposed to temperatures above 25°C/77°F or direct light and must be used within 14 days. Discard Xgeva if not used within the 14 days. Do not use Xgeva after the expiry date printed on the label.

Protect Xgeva from direct light and heat.

Avoid vigorous shaking of Xgeva.

17 PATIENT COUNSELING INFORMATION

Advise patients to contact a healthcare professional for any of the following:
- Symptoms of hypocalcemia, including paresthesias or muscle stiffness, twitching, spasms, or cramps *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*
- Symptoms of ONJ, including pain, numbness, swelling of or drainage from the jaw, mouth, or teeth *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*
- Persistent pain or slow healing of the mouth or jaw after dental surgery *[see Warnings and Precautions (5.2)]*
- Pregnancy or nursing *[see Use in Specific Populations (8.1, 8.3)]*

Advise patients of the need for:
- Proper oral hygiene and routine dental care
- Informing their dentist that they are receiving Xgeva
- Avoiding invasive dental procedures during treatment with Xgeva

Advise patients that denosumab is also marketed as Prolia™. Patients should inform their healthcare provider if they are taking Prolia.

AMGEN®

Xgeva™ (denosumab)

Manufactured by:
Amgen Manufacturing Limited, a subsidiary of Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

This product, its production, and/or its use may be covered by one or more US Patents, including US Patent Nos. 6,740,522; 7,411,050; 7,097,834; and 7,364,736, as well as other patents or patents pending.

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Appendix 2. Bone Metastasis-Free Survival by PSA Doubling Time of 10, 6, and 4 Months

Table 04-1.12.13. Bone Metastasis-Free Survival by PSA Doubling Time of 10 Months (Full Analysis Set) (Primary Analysis Data Set)

	Crude Incidence	KM Estimate of 25%-tile (Months)		KM Estimate of Median (Months)		Hazard Ratio[a]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
Overall (unadjusted)								
Placebo (N = 716)	370 (51.7)	11.1	(9.49, 11.37)	25.2	(22.18, 29.47)			
Denosumab 120 mg Q4W (N = 716)	335 (46.8)	11.3	(10.97, 14.72)	29.5	(25.40, 33.31)	0.85	(0.73, 0.98)	0.0284
Overall (adjusted for PSA doubling time)								
Placebo (N = 716)	370 (51.7)	11.1	(9.49, 11.37)	25.2	(22.18, 29.47)			
Denosumab 120 mg Q4W (N = 716)	335 (46.8)	11.3	(10.97, 14.72)	29.5	(25.40, 33.31)	0.85	(0.73, 0.98)	0.0295
PSA doubling time ≤ 10 months								
Placebo (N = 580)	309 (53.3)	11.1	(8.21, 11.30)	22.4	(21.68, 28.88)			
Denosumab 120 mg Q4W (N = 574)	273 (47.6)	11.2	(10.87, 14.06)	28.4	(24.84, 33.05)	0.84	(0.72, 0.99)	0.0423

n = Number of subjects with events;
N = Number of subjects randomized; KM = Kaplan-Meier
NE = Not estimable
Hazard ratio < 1 favors denosumab.
[a]Based on a Cox proportional hazards model with treatment groups as the independent variable and stratified by the randomization stratification factors
[b]Based on a Cox model adding subgroup and subgroup-by-treatment interaction to [a]

Program: /stat/amg162/b_mets/20050147/analysis/bla_2011pcprev_reg_prep/tables/program/t-bm-time-si-by.sas
Output: t04-01-012-013-bm-surv-si-by-psa10-l.rtf (Date Generated: 01DEC2011:15:33:36) Source Data: adam.asleff, adam.aslbase

Table 04-1.12.13. Bone Metastasis-Free Survival by PSA Doubling Time of 10 Months (Full Analysis Set) (Primary Analysis Data Set)

	Crude Incidence	KM Estimate of 25%-tile (Months)		KM Estimate of Median (Months)		Hazard Ratio[a]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
PSA doubling time > 10 months								
Placebo (N = 136)	61 (44.9)	11.5	(10.87, 15.87)	33.2	(22.18, NE)			
Denosumab 120 mg Q4W (N = 142)	62 (43.7)	15.0	(11.10, 18.69)	41.2	(22.31, NE)	0.90	(0.63, 1.29)	0.5659
Treatment-by-PSA doubling time interaction[b]								0.8008

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n = Number of subjects with events;
N = Number of subjects randomized; KM = Kaplan-Meier
NE = Not estimable
Hazard ratio < 1 favors denosumab.
[a]Based on a Cox proportional hazards model with treatment groups as the independent variable and stratified by the randomization stratification factors
[b]Based on a Cox model adding subgroup and subgroup-by-treatment interaction to [a]

Program: /stat/amg162/b_mets/20050147/analysis/bla_2011pcprev_reg_prep/tables/program/t-bm-time-si-by.sas
Output: t04-01-012-013-bm-surv-si-by-psa10-l.rtf (Date Generated: 01DEC2011:15:33:36) Source Data: adam.asleff, adam.aslbase

Table 04-1.3.13. Bone Metastasis-Free Survival by PSA Doubling Time of 6 Months (Full Analysis Set) (Primary Analysis Data Set)

	Crude Incidence	KM Estimate of 25%-tile (Months)		KM Estimate of Median (Months)		Hazard Ratio[a]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
Overall (unadjusted)								
Placebo (N = 716)	370 (51.7)	11.1	(9.49, 11.37)	25.2	(22.18, 29.47)			
Denosumab 120 mg Q4W (N = 716)	335 (46.8)	11.3	(10.97, 14.72)	29.5	(25.40, 33.31)	0.85	(0.73, 0.98)	0.0284
Overall (adjusted for PSA doubling time)								
Placebo (N = 716)	370 (51.7)	11.1	(9.49, 11.37)	25.2	(22.18, 29.47)			
Denosumab 120 mg Q4W (N = 716)	335 (46.8)	11.3	(10.97, 14.72)	29.5	(25.40, 33.31)	0.85	(0.73, 0.98)	0.0298
PSA doubling time ≤ 6 months								
Placebo (N = 427)	242 (56.7)	8.3	(7.39, 11.10)	18.7	(18.23, 22.31)			
Denosumab 120 mg Q4W (N = 419)	197 (47.0)	11.0	(7.89, 11.33)	25.9	(22.34, 31.64)	0.77	(0.64, 0.93)	0.0064

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n = Number of subjects with events;
N = Number of subjects randomized; KM = Kaplan-Meier
NE = Not estimable
Hazard ratio < 1 favors denosumab.
[a]Based on a Cox proportional hazards model with treatment groups as the independent variable and stratified by the randomization stratification factors
[b]Based on a Cox model adding subgroup and subgroup-by-treatment interaction to [a]

Program: /stat/amg162/b_mets/20050147/analysis/bla_2011pcprev_reg_prep/tables/program/t-bm-time-si-by.sas
Output: t04-01-003-013-bm-surv-si-by-psa6-l.rtf (Date Generated: 01DEC2011:15:33:36) Source Data: adam.asleff, adam.aslbase

Table 04-1.3.13. Bone Metastasis-Free Survival by PSA Doubling Time of 6 Months (Full Analysis Set) (Primary Analysis Data Set)

	Crude Incidence	KM Estimate of 25%-tile (Months)		KM Estimate of Median (Months)		Hazard Ratio[a]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
PSA doubling time > 6 months								
Placebo (N = 289)	128 (44.3)	14.8	(11.47, 18.60)	35.1	(29.01, 40.25)			
Denosumab 120 mg Q4W (N = 297)	138 (46.5)	14.8	(13.90, 17.54)	33.5	(23.29, 41.23)	1.00	(0.79, 1.28)	0.9898
Treatment-by-PSA doubling time interaction[b]								0.0819

n = Number of subjects with events;
N = Number of subjects randomized; KM = Kaplan-Meier
NE = Not estimable
Hazard ratio < 1 favors denosumab.
[a]Based on a Cox proportional hazards model with treatment groups as the independent variable and stratified by the randomization stratification factors
[b]Based on a Cox model adding subgroup and subgroup-by-treatment interaction to [a]

Program: /stat/amg162/b_mets/20050147/analysis/bla_2011pcprev_reg_prep/tables/program/t-bm-time-si-by.sas
Output: t04-01-003-013-bm-surv-si-by-psa6-l.rtf (Date Generated: 01DEC2011:15:33:36) Source Data: adam.asleff, adam.aslbase

Table 04-1.4.13. Bone Metastasis-Free Survival by PSA Doubling Time of 4 Months (Full Analysis Set) (Primary Analysis Data Set)

	Crude Incidence	KM Estimate of 25%-tile (Months)		KM Estimate of Median (Months)		Hazard Ratio[a]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
Overall (unadjusted)								
Placebo (N = 716)	370 (51.7)	11.1	(9.49, 11.37)	25.2	(22.18, 29.47)			
Denosumab 120 mg Q4W (N = 716)	335 (46.8)	11.3	(10.97, 14.72)	29.5	(25.40, 33.31)	0.85	(0.73, 0.98)	0.0284
Overall (adjusted for PSA doubling time)								
Placebo (N = 716)	370 (51.7)	11.1	(9.49, 11.37)	25.2	(22.18, 29.47)			
Denosumab 120 mg Q4W (N = 716)	335 (46.8)	11.3	(10.97, 14.72)	29.5	(25.40, 33.31)	0.85	(0.73, 0.99)	0.0316
PSA doubling time ≤ 4 months								
Placebo (N = 289)	167 (57.8)	7.4	(6.83, 9.59)	18.3	(14.85, 21.68)			
Denosumab 120 mg Q4W (N = 263)	124 (47.1)	10.8	(7.56, 11.30)	25.8	(18.99, 31.64)	0.71	(0.56, 0.90)	0.0044
PSA doubling time > 4 months								
Placebo (N = 427)	203 (47.5)	14.7	(11.30, 16.33)	31.2	(25.86, 36.60)			
Denosumab 120 mg Q4W (N = 453)	211 (46.6)	14.6	(11.20, 15.08)	33.1	(25.79, 38.28)	0.96	(0.79, 1.16)	0.6453

n = Number of subjects with events;
N = Number of subjects randomized; KM = Kaplan-Meier
NE = Not estimable
Hazard ratio < 1 favors denosumab.
[a]Based on a Cox proportional hazards model with treatment groups as the independent variable and stratified by the randomization stratification factors
[b]Based on a Cox model adding subgroup and subgroup-by-treatment interaction to [a]

Program: /stat/amg162/b_mets/20050147/analysis/bla_2011pcprev_reg_prep/tables/program/t-bm-time-by-psa.sas
Output: t04-01-004-013-bm-surv-by-psa4-l.rtf (Date Generated: 16DEC2011:11:47:05) Source Data: adam.asleff, adam.aslbase

Table 04-1.4.13. Bone Metastasis-Free Survival by PSA Doubling Time of 4 Months (Full Analysis Set) (Primary Analysis Data Set)

	Crude Incidence	KM Estimate of 25%-tile (Months)		KM Estimate of Median (Months)		Hazard Ratio[a]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
Treatment-by-PSA doubling time interaction[b]								0.0500
Qualitative interaction by Gail and Simon test								0.5000

n = Number of subjects with events;
N = Number of subjects randomized; KM = Kaplan-Meier
NE = Not estimable
Hazard ratio < 1 favors denosumab.
[a]Based on a Cox proportional hazards model with treatment groups as the independent variable and stratified by the randomization stratification factors
[b]Based on a Cox model adding subgroup and subgroup-by-treatment interaction to [a]

Program: /stat/amg162/b_mets/20050147/analysis/bla_2011pcprev_reg_prep/tables/program/t-bm-time-by-psa.sas
Output: t04-01-004-013-bm-surv-by-psa4-l.rtf (Date Generated: 16DEC2011:11:47:05) Source Data: adam.asleff, adam.aslbase

Appendix 3. Analysis of Time to First Non-bone Metastasis or Death and Analysis of Patterns of Metastasis to Non-osseous Sites

Additional analyses from Study 20050147 have been performed to examine the time to first non-bone metastasis or death and the pattern of non-bone metastases. This document describes the results of these analyses and outlines their limitations.

Time to First Non-bone Metastasis or Death

When considering the analysis of time to non-bone metastasis or death, it is important to note that the study was focused on evaluating the effect of denosumab on bone metastases. The exclusion criteria therefore ensured that the subjects enrolled in the study had no evidence of bone metastases at study entry. Although Study 20050147 excluded subjects with distant organ metastases, metastases to any lymph node region, per protocol, were specifically allowed (but were not stratified) and locally progressive disease was not specifically excluded. These eligibility criteria were chosen for practical reasons to avoid the necessity of obtaining biopsy proof of locally progressive or lymph node metastatic disease.

Potentially relevant imbalances against denosumab in the prostate cancer history that may have affected the development of non-bone metastases include more subjects with high Gleason score, more subjects with lymph node metastatic disease, and more subjects with T3 - T4 disease. Further, fewer subjects randomized to denosumab had local treatment of the primary tumor and more subjects randomized to denosumab received chemotherapy prior to study entry (Table 1).

It is important to note that subjects were required to discontinue treatment and study when a bone metastasis was confirmed by the central reader. Since more placebo-treated subjects developed a bone metastasis on study, more subjects in the placebo group than in the denosumab group discontinued the study due to bone metastases. These subjects were therefore not available for further follow-up for development of metastases in non-bone sites. Conversely, fewer subjects on the denosumab arm discontinued the study due to bone metastases and were therefore available for a longer observation period compared to those subjects in the placebo group. This difference in study discontinuation results in potential informative censoring, which limits interpretation of the analysis of non-bone metastasis or death. As a result, the analyses in the 20050147 CSR on disease progression and progression-free survival, which include disease progression to bone and non-bone sites, provide the most reliable information to assess disease progression in the study population.

Time to first non-bone metastasis or death was similar between treatment groups (hazard ratio [95% CI] of 1.07 [0.88, 1.30]; p-value = 0.5275) (Table 2). Adjusting for additional covariates of regional lymph node at diagnosis, current lymphatic metastasis, T3 –T4 disease, primary local therapy, and prior chemotherapy, the analysis of time to first non-bone metastasis or death resulted in a hazard ratio of 1.03 ([0.85, 1.25], p-value = 0.779) (Table 3). A total of 215 (30.0%) and 191 (26.7%) subjects in the denosumab and placebo treatment groups, respectively, developed a non-bone metastasis or died during the primary blinded treatment phase (Table 2).

Table 1. Baseline Key Characteristics and Disease History (Full Analysis Set) (20050147 for Primary Analysis)

	Placebo (N = 716)	Denosumab 120 mg Q4W (N = 716)	All (N = 1432)
Primary tumor at diagnosis - n (%)			
T0 or T1 - T2a	132 (18.4)	122 (17.0)	254 (17.7)
T2 or T2b - T2c	217 (30.3)	231 (32.3)	448 (31.3)
T3 or T3a	217 (30.3)	214 (29.9)	431 (30.1)
T3b - T4	85 (11.9)	98 (13.7)	183 (12.8)
Tx	65 (9.1)	51 (7.1)	116 (8.1)
Regional lymph node at diagnosis - n (%)			
N0	331 (46.2)	331 (46.2)	662 (46.2)
N1	68 (9.5)	87 (12.2)	155 (10.8)
Nx	317 (44.3)	298 (41.6)	615 (42.9)
Presence of distant metastasis at diagnosis - n (%)			
M0	570 (79.6)	566 (79.1)	1136 (79.3)
M1	4 (0.6)	5 (0.7)	9 (0.6)
Mx	142 (19.8)	145 (20.3)	287 (20.0)
Gleason score at diagnosis - n (%)			
2-7	432 (60.3)	404 (56.4)	836 (58.4)
8-10	214 (29.9)	237 (33.1)	451 (31.5)
Missing	70 (9.8)	75 (10.5)	145 (10.1)

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N = Number of subjects randomized
Percentages based on number of subjects randomized

Source: CSR 20050147, Tables 14-2.25 and 14-2.25.1

**Table 1. Baseline Key Characteristics and Disease History
(Full Analysis Set)
(20050147 for Primary Analysis)**

	Placebo (N = 716)	Denosumab 120 mg Q4W (N = 716)	All (N = 1432)
Current lymphatic metastasis - n (%)			
Yes	88 (12.3)	93 (13.0)	181 (12.6)
No	628 (87.7)	623 (87.0)	1251 (87.4)
Type of primary local therapy			
Radiation	217 (30.3)	189 (26.4)	406 (28.4)
Surgery	56 (7.8)	46 (6.4)	102 (7.1)
Surgery and Radiation	58 (8.1)	78 (10.9)	136 (9.5)
No primary therapy	385 (53.8)	403 (56.3)	788 (55.0)
Prior chemotherapy - n (%)			
Yes	54 (7.5)	63 (8.8)	117 (8.2)
No	662 (92.5)	653 (91.2)	1315 (91.8)

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N = Number of subjects randomized
Percentages based on number of subjects randomized

Source: CSR 20050147, Tables 14-2.25 and 14-2.25.1

Table 2. Non Bone Metastasis Free Survival
(Full Analysis Set)
(20050147 for Primary Analysis)

	Crude Incidence	KM Estimate of 25%-tile (Days)[a]		KM Estimate of Median (Days)[a]		Hazard Ratio[b]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
Placebo (N = 716)	191 (26.7)	639.0	(561.00, 718.00)	NE	(1380.00, NE)			
Denosumab 120 mg Q4W (N = 716)	215 (30.0)	550.0	(453.00, 638.00)	NE	(1325.00, NE)	1.07	(0.88, 1.30)	0.5275

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n = Number of subjects with events
N = Number of subjects randomized
Non Bone Metastasis includes non-bone prostate cancer disease progression determined by investigators
[a] Kaplan-Meier estimate
[b] Based on the Cox proportional hazards model with treatment, age, race, prior prostatectomy and/or radiation therapy, Gleason score, time from initiation of ADT (including orchiectomy, or chemical castration) to randomization, time from diagnosis to randomization, and ECOG as the independent variables and stratified by the randomized stratification factors
Hazard ratio < 1 favors denosumab.

Program: /stat/amg162/b_mets/20050147/analysis/final/adhoc/program/t_ah_nbm_surv_si.sas
Output: t14-04_004_561_ah_nbm_surv_si.rtf (Date Generated: 13APR2011: 9:13:40) Source Data: adam.asleff, adam.aslbase

Table 3. Non Bone Metastasis Free Survival Adjusting for Additional Covariates (Full Analysis Set)

	Crude Incidence	KM Estimate of 25%-tile (Days)[a]		KM Estimate of Median (Days)[a]		Hazard Ratio[b]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
Placebo (N = 716)	191 (26.7)	639.0	(561.00, 718.00)	NE	(1380.00, NE)			
Denosumab 120 mg Q4W (N = 716)	215 (30.0)	550.0	(453.00, 638.00)	NE	(1325.00, NE)	1.03	(0.85, 1.25)	0.7790

n = Number of subjects with events
N = Number of subjects randomized
Non Bone Metastasis includes non-bone prostate cancer disease progression determined by investigators
[a] Kaplan-Meier estimate
[b] Based on the Cox proportional hazards model with treatment, age, race, prior prostatectomy and/or radiation therapy, Gleason score, time from initiation of ADT (including orchiectomy, or chemical castration) to randomization, time from diagnosis to randomization, ECOG , regional lymph node at diagnosis, current lymphatic metastasis, T3/T4 primary tumor at diagnosis, primary local therapy and prior chemotherapy as the independent variables and stratified by the randomized stratification factors
Hazard ratio < 1 favors denosumab.

Source: Table 100-1.10

Program: /stat/amg162/meta/bla_2011pcprev/analysis/reg_quest/tables/program/t-fda-20111216-nbm-surv-si.sas
Output: t100-01-010-fda-20111216-nbm-surv-si-l.rtf (Date Generated: 22DEC2011:20:06:33) Source Data: paadam.asleff, paadam.aslinfo, paadam.aslbase, pasdtm.df, pasdtm.suppdf

Patterns of Metastasis to Non-bone Sites

The analysis of the pattern of first metastases at non-bone sites reported by investigators is presented in Table 4.

Numerical differences between arms in Table 4 were observed for primarily lymph node sites, particularly pelvic lymph nodes, and lung metastases, although the number of subjects with extra-skeletal progression at each of these sites is small.

Table 4. Distribution of the First Extra-Skeletal Metastasis
(Full Analysis Set)
(Primary Analysis Data Set)

	Placebo (N=716) n (%)	Denosumab 120 mg Q4W(N=716) n (%)
Number of subjects with extraskeletal progression	156	184
Other	88 (56.4)	84 (45.7)
Lymph nodes - pelvic site	16 (10.3)	27 (14.7)
Lymph nodes - retroperitoneum	18 (11.5)	25 (13.6)
Lymph nodes - abdomen	17 (10.9)	19 (10.3)
Lung	7 (4.5)	15 (8.2)
Liver	8 (5.1)	12 (6.5)
Brain	1 (0.6)	1 (0.5)
Pleura	1 (0.6)	1 (0.5)

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N = Number of subjects randomized
Percentage based on the number of subjects with extraskeletal progression
For subjects with progression at multiple sites on the same day, first progression site was selected according to the following order: brain, liver, lung, pleura, and lymph nodes at abdomen, lymph nodes at retroperitoneum, lymph nodes at pelvic site, and other.
Sorted by descending order of frequency in the denosumab group.

Program: /stat/amg162/meta/bla_2011pcprev/analysis/reg_quest/tables/program/t-fda-20111216-extraskel-first-prog.sas
Output: t100-01-009-fda-20111216-extraskel-first-prog-p.rtf (Date Generated: 22DEC2011:11:12:26) Source Data: paadam.aslinfo, pasdtm.df, pasdtm.suppdf

Appendix 4. Listing of MedDRA v. 13.1 Preferred Terms That Triggered Acute Coronary Syndrome Adjudication and Subject Listing of Adjudicated Positive Acute Coronary Syndrome Adverse Events

Listing 1. List of MedDRA v. 13.1 Preferred Terms that Triggered Acute Coronary Syndrome Adjudication

MedDRA Preferred Term		
Acute coronary syndrome	Cardiac telemetry abnormal	Coronary artery restenosis
Acute myocardial infarction	Cardiac ventriculogram abnormal	Coronary artery stenosis
Angina pectoris	Cardiac ventriculogram left abnormal	Coronary artery bypass
Angina unstable	Cardiac ventriculogram right abnormal	Coronary artery thrombosis
Angiogram abnormal	Cardio-respiratory arrest	Coronary bypass thrombosis
Arterial catheterisation abnormal	Cardiovascular disorder	Coronary endarterectomy
Arteriogram abnormal	Cardiovascular function test abnormal	Coronary no-reflow phenomenon
Arteriogram coronary abnormal	Catheterisation cardiac abnormal	Coronary ostial stenosis
Arteriosclerosis coronary artery	Chest discomfort	Coronary revascularisation
Arteriospasm coronary	Chest pain	Dissecting coronary artery aneurysm
Arteritis coronary	Computerised tomogram coronary artery abnormal	Dressler's syndrome
Blood creatine phosphokinase abnormal	Coronary angioplasty	ECG signs of myocardial ischaemia
Blood creatine phosphokinase increased	Coronary arterial stent insertion	Electrocardiogram abnormal
Blood creatine phosphokinase MB	Coronary artery aneurysm	Electrocardiogram poor R-wave progression
Blood creatine phosphokinase MB abnormal	Coronary artery dilatation	Electrocardiogram Q wave abnormal
Blood creatine phosphokinase MB increased	Coronary artery disease	Electrocardiogram QRS complex abnormal
Cardiac death	Coronary artery dissection	Electrocardiogram QRS complex prolonged
Cardiac disorder	Coronary artery embolism	Electrocardiogram QT interval abnormal
Cardiac enzymes increased	Coronary artery insufficiency	Electrocardiogram QT prolonged
Cardiac function test abnormal	Coronary artery occlusion	Electrocardiogram ST segment abnormal
Cardiac imaging procedure abnormal	Coronary artery perforation	Electrocardiogram ST segment depression
Cardiac stress test abnormal	Coronary artery reocclusion	Electrocardiogram ST segment elevation

Listing 1. List of MedDRA v. 13.1 Preferred Terms that Triggered Acute Coronary Syndrome Adjudication

MedDRA Preferred Term		
Electrocardiogram ST-T change	Infarction	
Electrocardiogram ST-T segment abnormal	Ischaemia	Prinzmetal angina
Electrocardiogram ST-T segment depression	Microvascular angina	Pulse volume decreased
Electrocardiogram ST-T segment elevation	Multiple gated acquisition scan abnormal	QRS axis abnormal
Electrocardiogram T wave abnormal	Myocardial depression	Scan myocardial perfusion abnormal
Electrocardiogram T wave amplitude decreased	Myocardial infarction	Silent myocardial infarction
Electrocardiogram T wave amplitude increased	Myocardial ischaemia	Stress echocardiogram abnormal
Electrocardiogram T wave biphasic	Myocardial reperfusion injury	Subendocardial ischaemia
Electrocardiogram T wave inversion	Papillary muscle disorder	Sudden cardiac death
Electrocardiogram T wave peaked	Papillary muscle haemorrhage	Sudden death
Endocardial varices	Papillary muscle infarction	Troponin I increased
Exercise electrocardiogram abnormal	Papillary muscle rupture	Troponin increased
Exercise test abnormal	Percutaneous coronary intervention	Troponin T increased
Haemorrhage coronary artery	Postinfarction angina	Ventricle rupture

Listing 2. Subject Listing of Adjudicated Positive Acute Coronary Syndrome Adverse Events
(Safety Analysis Set)
(20050147 Blinded Treatment Analysis)

Subject Identification Number	Preferred Term
Placebo	
147185011	Coronary Artery Stenosis
147225004	Myocardial Infarction
147228004	Chest Pain
147261001	Myocardial Infarction
147300008	Myocardial Infarction
147309004	Acute Myocardial Infarction
147331025	Myocardial Infarction
147335003	Myocardial Infarction
147640003	Myocardial Infarction
147678001	Coronary Artery Stenosis
147718006	Coronary Artery Thrombosis
147733007	Acute Myocardial Infarction
147907007	Myocardial Infarction
Denosumab	
147283015	Myocardial Infarction
147335006	Myocardial Infarction
147510001	Myocardial Infarction
147510003	Myocardial Infarction
147510007	Angina Pectoris
147639005	Myocardial Infarction
147654001	Myocardial Infarction
147713003	Acute Myocardial Infarction
147771006	Angina Pectoris
147792008	Myocardial Ischemia
147792011	Acute Myocardial Infarction
147822002	Myocardial Ischemia
147854008	Angina Pectoris
147913003	Myocardial Infarction

Source: Listing 01-01-001-ae-acs

Note: Both non-fatal and fatal acute coronary syndrome events reported using the same preferred term were adjudicated positive for subjects 147309004, 147335003, and 147718006.